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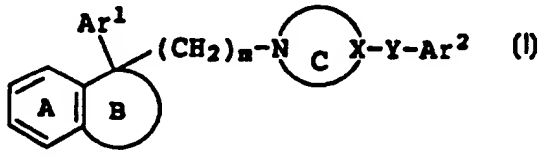
(54) Title: BICYCLIC COMPOUNDS FOR CONTROLLING MICTURITION

(57) Abstract

A compound of formula (I), wherein ring A represents a benzene ring which may be substituted; ring B represents a 4- to 7-membered carbocyclic or heterocyclic ring which may be substituted; ring C represents a nitrogen-containing heterocyclic ring which may be substituted; X represents a carbon atom or a nitrogen atom; Y represents a bond or a lower alkylene group which may be substituted by an oxo; each of Ar^1 and Ar^2 represents an aromatic group which may be substituted; m represents an integer of 1 to 3; or a salt thereof is useful for controlling micturition.



(I)

DESCRIPTION

BICYCLIC COMPOUNDS FOR CONTROLLING MICTURITION

TECHNICAL FIELD

The present invention relates to bicyclic compounds, their production and use, especially a pharmaceutical composition for controlling micturition.

BACKGROUND ART

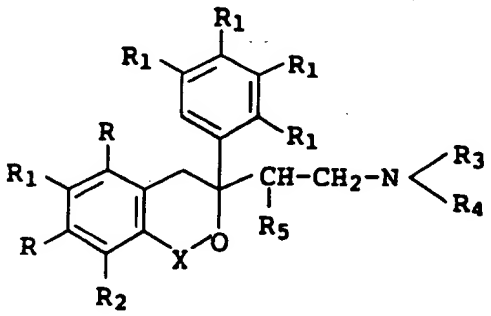
The term, lower urinary tract dysfunctions, generically refers to the subjective or objective abnormalities in the process from urine accumulation to excretion, including urine storage disorders (urinary incontinence, pollakiuria etc.) and voiding dysfunctions (dysuria, micturition pain, urethral obstruction etc.). Although lower urinary tract dysfunctions are found from young age, lower urinary tract dysfunctions, especially urine storage disorders, in the elderly, have recently posed a major social problem with the development of aging society.

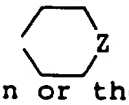
The mechanism of micturition consists of contraction-relaxation of the urinary bladder, where urine is reserved for a given period of time, the urethral neck, which controls excretion, and the urethra. Micturition is controlled by the peripheral nervous system, which comprises the parasympathetic nervous system, including the pelvic nerve, and the sympathetic nerves, including the hypogastric nerve, under the control of the micturition center, and has been suggested as mediated by various nerve transmitters (e.g., acetylcholine, adrenaline, ATP, substance P, neuropeptide Y).

On the other hand, for the treatment of urinary incontinence or pollakiuria, there has been reported an indole-2-carboxyanilide derivative represented by the formula:

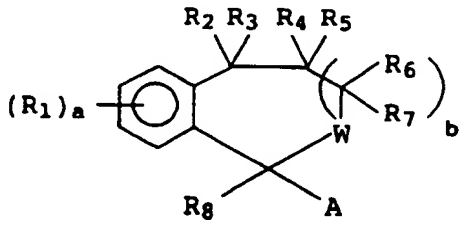
N; possesses gonadotropin-releasing hormone receptor-antagonizing activity, monoamine uptake-inhibiting activity and calcium ion uptake-inhibiting activity.

2) USP 3,880,885 describes that a compound represented by the formula:



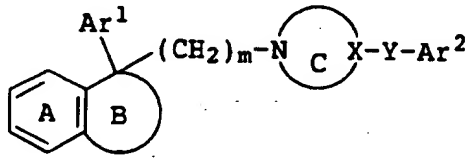
wherein R represents hydrogen or the like; R_1 represents hydrogen or the like; R_2 represents hydrogen or the like; each of R_3 and R_4 represents a lower alkyl or the like, or they cooperate with each other to form $-(CH_2)_n-$ (n is 4 to 7) or  ; Z represents O, S or N-R_6; R_5 represents hydrogen or the like; R_6 represents a lower alkyl; X represents $-CH_2-$ or -CO-; possesses diuretic activity.

3) USP 4,247,553 describes that a compound represented by the formula:



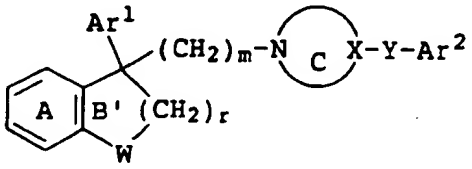
wherein R_1 represents a C_{1-3} alkyl or the like; a is 1 to 3; b is 0 or 1; each of R_2 through R_7 represents a C_{1-3} alkyl or the like; R_8 represents a phenyl or the like; W represents O or S; A represents $-(CH_2)_nNR_9R_{10}$ or the like;

The present inventors conducted various investigations of compounds that potentially control micturition, and for the first time found that a compound represented by the formula:



(I)

wherein ring A represents a benzene ring which may be substituted; ring B represents a 4- to 7-membered carbocyclic or heterocyclic ring which may be substituted; ring C represents a nitrogen-containing heterocyclic ring which may be substituted; X represents a carbon atom or a nitrogen atom; Y represents a bond or a lower alkylene group which may be substituted by an oxo; each of Ar^1 and Ar^2 represents an aromatic group which may be substituted; m represents an integer from 1 to 3; or a salt thereof [hereinafter also referred to as compound (I)], especially a new compound represented by the formula:



(Ia)

wherein ring B' represents a 5- to 7-membered carbocyclic or heterocyclic ring which may be substituted; W represents a divalent group represented by the formula: $-CH_2-CH_2-$, $-CH=CH-$, $-CO-O-$, $-CO-NR^6-$, $-NR^6-CO-$, $-N=CH-$, $-CH_2-S(O)_p-$, $-N=N-$, $-NR^6-SO_2-$, $-SO_2-NR^6-$, $-NR^6-NR^{6a}-$, $-CH_2-NR^6-CO-$ or $-CO-NR^6-CO-$ (each of R^6 and R^{6a} represents a hydrogen atom, a hydrocarbon group which may be substituted, an acyl or an amino which may be substitut d; p represents an integer from 0 to 2); r represents an integer from 0 to 2; the

ring B is a 4- to 7-membered carbocyclic or h terocyclic ring optionally containing 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino, di-C_{7-16} aralkylamino and oxo;
ring C is a 4- to 7-membered nitrogen-containing heterocyclic ring containing at least one nitrogen atom which may be oxidized, in addition to carbon atoms, and optionally containing 1 to 3 hetero atoms selected from oxygen, nitrogen and sulfur atoms, which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl,

(6) the composition of above (1), which is for the prophylaxis or treatment of the lower urinary tract dysfunctions,

(7) the composition of above (6), wherein the lower urinary tract dysfunctions is urinary incontinence or pollakiuria,

(8) compound (Ia),

(9) the compound of above (8), wherein R^6 and R^{6a} each is (i) a hydrogen atom,

(ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, (7) optionally halogenated C_{1-6} alkoxy, (8) optionally halogenated C_{1-6} alkylthio, (9) hydroxy, (10) amino, (11) mono-C_{1-6} alkylamino, (12) di-C_{1-6} alkylamino, (13) 3- to 7-membererd saturated cyclic amino, (14) formyl, (15) acyl, (16) acylamino, (17) carboxy, (18) carbamoyl, (19) sulfo, (20) sulfamoyl, (21) mono-C_{1-6} alkylsulfamoyl, (22) di-C_{1-6} alkylsulfamoyl, (23) C_{6-10} aryl which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6}

optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, (28) C_{1-6} alkoxy-C_{1-6} alkoxy, (29) mono-C_{7-16} aralkylamino and (30) di-C_{7-16} aralkylamino; the C_{3-6} cycloalkyl may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen, sulfur and nitrogen atoms in addition to carbon atoms,

(iii) an acyl represented by the formula: $-(C=O)-R^1$, $-(C=O)-NR^1R^2$, $-(C=S)-NHR^1$, $-(C=O)-OR^1$, $-SO_2-R^1$ or $-SO-R^1$ wherein R^1 is (iii-1) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, (7) optionally halogenated C_{1-6} alkoxy, (8) optionally halogenated C_{1-6} alkylthio, (9) hydroxy, (10) amino, (11) mono-C_{1-6} alkylamino, (12) di-C_{1-6} alkylamino, (13) 3- to 7-membererd saturated cyclic amino, (14) formyl, (15) acyl, (16) acylamino, (17) carboxy, (18) carbamoyl, (19) sulfo, (20) sulfamoyl, (21) mono-C_{1-6} alkylsulfamoyl, (22) di-C_{1-6} alkylsulfamoyl, (23) C_{6-10} aryl which may be substituted by 1 to 5 substituents selected from th group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl,

alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, (26) acyloxy, (27) phthalimido which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, (28) C_{1-6} alkoxy-C_{1-6} alkoxy, (29) mono-C_{7-16} aralkylamino and (30) di-C_{7-16} aralkylamino, or

(iii-2) a 5- to 10-membered heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo,

C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, (24) C_{6-10} aryloxy which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, (25) 5- to 10-membered aromatic heterocyclic group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, (26) acyloxy, (27) phthalimido which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated

(12) the compound of above (8), wherein ring A is a benzene ring which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, optionally halogenated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy,

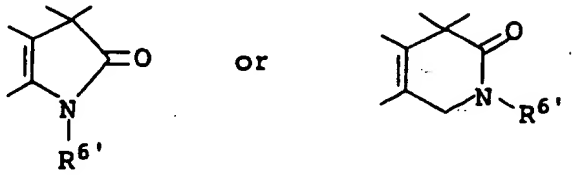
(13) the compound of above (8), wherein ring C is a 6-membered nitrogen-containing heterocyclic ring containing 1 or 2 nitrogen atoms which may be oxidized, in addition to carbon atoms, which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl and carboxy,

(14) the compound of above (8), wherein Y is a bond or a methylene,

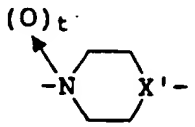
(15) the compound of above (8), wherein Ar^1 is a phenyl or 5- or 6-membered aromatic heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, optionally halogeneated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy,

(16) the compound of above (8), wherein Ar^2 is a phenyl or 5- or 6-membered aromatic heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6}

(19) the compound of above (8), wherein ring A is an optionally halogenated benzene ring;
ring B' is a ring of the formula:

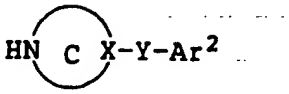


wherein $R^{6'}$ is (i) a hydrogen atom,
(ii) a C_{1-6} alkyl, C_{2-6} alkenyl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents selected from th group consisting of halogen, cyano, 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, hydroxy, amino, mono- or di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, C_{1-6} alkoxy-carbonyl, C_{1-6} alkyl-carbonyloxy, phthalimido and C_{1-6} alkoxy-C_{1-6} alkoxy,
(iii) a C_{1-6} alkyl-carbonyl, or
(iv) a mono- or di-C_{1-6} alkylamino, a mono- or di-C_{7-16} aralkylamino or a 3- to 7-membered saturated cyclic amino,
ring C is a ring of the formula:



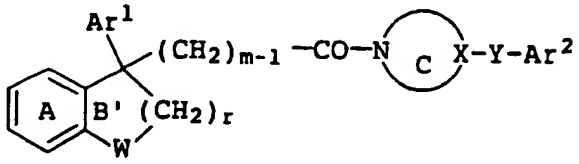
wherein X' is (i) a nitrogen atom or (ii) a group of the formula: $>C(R^{5'})-$
wherein $R^{5'}$ is a hydrogen atom, cyano, hydroxy or C_{1-6} alkyl-carbonyl, and t is 0 or 1,
Y is a bond,
Ar^1 is a phenyl,
Ar^2 is a phenyl or pyridyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, nitro, cyano, optionally halogenated C_{1-6} alkyl,

wherein L represents a leaving group and the other symbols are as defined above, or a salt thereof with a compound of the formula;



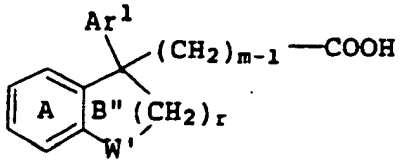
wherein all symbols are as defined above, or a salt thereof or

(ii) subjecting a compound of the formula:



wherein all symbols are as defined above, or a salt thereof to reduction,

(22) an optical isomer of the formula:



wherein ring A represents an optionally substituted benzene ring;

ring B" represents an optionally substituted 5- to 7-membered carbocyclic or heterocyclic ring;

W' represents a divalent group of the formula: $-CH_2-CH_2-$, $-CH=CH-$, $-CO-O-$, $-CO-NR^6-$, $-NR^6-CO-$, $-N=CH-$, $-CH_2-S(O)_p-$, $-N=N-$, $-NR^6-SO_2-$, $-SO_2-NR^6-$, $-NR^6-NR^{6a}-$, $-CH_2-O-$, $-CH_2-NR^6-$, $-NR^6-CH_2-$, $-CH=N-$, $-CH_2-NR^6-CO-$ or $-CO-NR^6-CO-$

wherein R^6 and R^{6a} each represents a hydrogen atom, an optionally substituted hydrocarbon group, acyl or an optionally substituted amino, and p represents an integer of 0 to 2;

halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, dibutylamino), 3- to 7-membered saturated cyclic amino (e.g., morpholino, thiomorpholino, piperazin-1-yl, 4-substituted-piperazin-1-yl, piperidino, pyrrolidin-1-yl), formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl (e.g., methylsulfamoyl, ethylsulfamoyl), di-C_{1-6} alkylsulfamoyl (e.g., dimethylsulfamoyl, diethylsulfamoyl), C_{6-10} aryl (e.g., phenyl, naphthyl), C_{6-10} aryloxy (e.g., phenyloxy, naphthyloxy), acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy (e.g., methoxymethoxy, 2-methoxyethoxy, 3-methoxypropoxy), mono-C_{7-16} aralkylamino (e.g., benzylamino, phenethylamino, 1-naphthylamino, 2-naphthylamino, 3-phenylpropylamino), di-C_{7-16} aralkylamino (e.g., dibenzylamino, diphenethylamino).

The above-described "optionally halogenated C_{1-6} alkyl" includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine). Specifically, such alkyl includes methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl and 6,6,6-trifluorohexyl.

trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio and hexylthio.

The "substituent" for the above-described "4-substituted-piperazin-1-yl" includes, for example, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl), C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl), C_{6-10} aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl), mono-C_{1-6} alkyl-carbamoyl (e.g., methylcarbnamoyl, ethylcarbamoyl), di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl) and mono-C_{6-10} aryl-carbamoyl (e.g., phenylcarbamoyl).

The above-described "acyl" includes, for example, an acyl represented by the formula: $-(C=O)-R^1$, $-(C=O)-NR^1R^2$, $-(C=O)-OR^1$, $-(C=S)-NHR^1$, $-SO_2-R^1$ or $-SO-R^1$ wherein R^1 represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; R^2 represents a hydrogen atom or a C_{1-6} alkyl; or R^1 and R^2 may form, taken together with the adjacent nitrogen atom, a nitrogen-containing heterocyclic ring. Among others, the acyl represented by the formula: $-(C=O)-R^1$, $-(C=O)-NR^1R^2$, $-(C=O)-OR^1$, $-SO_2-R^1$, $-SO-R^1$, or the like wherein the symbols have the same definitions as those shown above, is preferred. More preferable acyl includes, for example, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl), C_{6-10} aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl), C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl), mono-C_{1-6} alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl), di-C_{1-6} alkylcarbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, N-ethyl-N-methylcarbamoyl), C_{6-10} arylcarbamoyl which may be substituted, C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl) and C_{6-10} arylsulfonyl (e.g., phenylsulfonyl, naphthylsulfonyl). The above-described "C_{6-10} arylcarbamoyl which may be substituted" includes, for example, phenylcarbamoyl and

carbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy), di-C_{1-6} alkyl-carbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy), C_{6-10} aryl-carbamoyloxy (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy) and nicotinoyloxy.

The "hydrocarbon group which may be substituted" represented by R^1, R^3, R^{3a} or R^{3c} is a group resulting from removal of one hydrogen atom from a hydrocarbon compound, and is exemplified by chain or cyclic hydrocarbon group (e.g., alkyl, alkenyl, cycloalkyl, aryl, aralkyl). Of the hydrocarbon group, the following chain or cyclic hydrocarbon group having 1 to 16 carbon atoms, etc. is preferred.

a) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl),

b) C_{2-6} alkenyl (e.g., vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl),

c) C_{2-6} alkynyl (e.g., ethynyl, propargyl, butynyl, 1-hexynyl),

d) C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl),

e) C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-indenyl, 2-anthryl), preferably phenyl,

f) C_{7-16} aralkyl (e.g., benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl), preferably benzyl.

Of the hydrocarbon group, C_{1-6} alkyl, C_{6-14} aryl and C_{7-16} aralkyl are preferred.

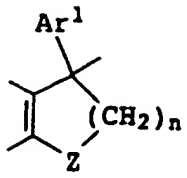
The "substituent" for the "hydrocarbon group which may be substituted" is exemplified by a halogen atom (e.g., fluorine, chlorine, bromine, iodine), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy), nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenat d 3- to 6-member d cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen

"acyl" in the "acyl", "acylamino" and "acyloxy", it is preferable that R^1 in the above-described formulas: $-(C=O)-R^1$, $-(C=O)-NR^1R^2$, $-(C=O)-OR^1$, $-(C=S)-NHR^1$, $-(C=O)-OR^1$, $-SO_2-R^1$ and $-SO-R^1$ be (i) a hydrocarbon group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen atom, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, 5- to 10-membered aromatic heterocyclic group, phthalimido, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, or (ii) a heterocyclic group which may be substituted 1 to 5 substituents selected from the group consisting of a halogen atom, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, optionally halogenated di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino.

The above-described "5- to 10-membered aromatic heterocyclic group which may be substituted" is exemplified by 5- to 10-membered aromatic heterocyclic group selected

Provided that 2 or more substituents are present, they may be identical or not.

With respect to the "acyl" in the "acyl", "acylamino" and "acyloxy" as a "substituent" for the above-described "heterocyclic group which may be substituted", it is preferable that R^1 in the above-described formulas: $-(C=O)-R^1$, $-(C=O)-NR^1R^2$, $-(C=O)-OR^1$, $-(C=S)-NHR^1$, $-SO_2-R^1$ and $-SO-R^1$ is (i) a hydrocarbon group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen atom, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, 5- to 10-membered aromatic heterocyclic group, phthalimido, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, or (ii) a heterocyclic group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen atom, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10}



wherein Ar^1 has the same definition as that shown above; n represents an integer from 0 to 2; Z represents the formula: $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-O-$, $-CO-O-$, $-CH_2-NR^4-$, $-NR^4-CH_2-$, $-CO-NR^4-$, $-NR^4-CO-$, $-CH=N-$, $-N=CH-$ or $-CH_2-S(O)_p-$ wherein R^4 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl; p represents an integer from 0 to 2.

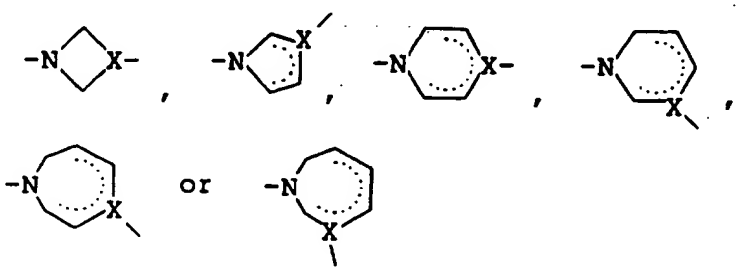
The "hydrocarbon group" for the "hydrocarbon group which may be substituted" represented by R^4 is identical to the "hydrocarbon group" represented by R^1, R^3, R^{3a} or R^{3c} above and the C_{3-6} cycloalkyl may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen, sulfur and nitrogen atoms in addition to carbon atoms.

The "substituent" for the "hydrocarbon group which may be substituted" represented by R^4 is identical to the "substituent" of the "hydrocarbon group which may be substituted" represented by R^1, R^3, R^{3a} or R^{3c} above.

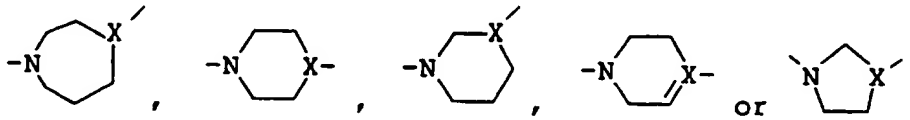
Of the "hydrocarbon group which may be substituted", preference is given to C_{1-6} alkyl or C_{7-16} aralkyl (preferably C_{1-6} alkyl) which may be substituted by 1 to 3 substituents selected from a halogen atom, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxy, carbamoyl, C_{1-6} alkoxy-carbonyl, cyano, C_{3-6} cycloalkyl, epoxyethyl, C_{1-6} alkoxy, 3- to 7-membered saturated cyclic amino, C_{1-6} alkyl-carbonyl and phthalimido.

The "acyl" represented by R^4 is identical to the "acyl" d scrib d in detail as the "substituent" for the "benzene ring which may be substituted" represented by ring

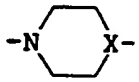
containing at least one nitrogen atom in addition to carbon atoms and may containing 1 to 3 hetero atoms selected from oxygen, nitrogen and sulfur atoms. Among others, preferred is a 6-membered nitrogen-containing heterocyclic ring. Specifically, such nitrogen-containing heterocyclic ring includes the ring represented by the formula:



wherein ⋯ represents a single bond or a double bond; X is as defined above. More preferable nitrogen-containing heterocyclic ring includes the ring represented by the formula:



wherein, X is as defined above. Still more preferable nitrogen-containing heterocyclic ring includes the ring represented by the formula:



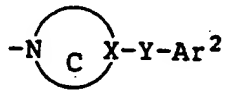
wherein X is as defined above.

X is preferably (i) a nitrogen atom or (ii) a group represented by the formula: $>C(R^5)-$ wherein R^5 represents a hydrogen atom, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated

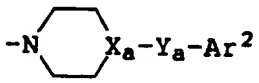
at any possible position. Specifically, such alkylene includes methylene, carbonyl, ethylene, trimethylene, propylene and tetramethylene.

Y is preferably a bond or methylene. More preferred is a bond.

The group represented by the formula:



wherein the symbols have the same definitions as those shown above, is preferably a group represented by the formula:



wherein Xa represents (i) a nitrogen atom or (ii) a group represented by the formula: $>C(R^{5a})-$ wherein R^{5a} represents a hydrogen atom, cyano, an optionally halogenated C_{1-6} alkyl, an optionally halogenated C_{1-6} alkoxy, an optionally halogenated C_{1-6} alkylthio, hydroxy, amino, a mono-C_{1-6} alkylamino, a di-C_{1-6} alkylamino, carboxy, a C_{1-6} alkoxy-carbonyl, a C_{1-6} alkyl-carbonylamino or a C_{1-6} alkyl-carbonyl; Ya represents a bond or methylene; Ar^2 is as defined above.

The "aromatic group which may be substituted" represented by Ar^1 or Ar^2 is exemplified by an aromatic hydrocarbon group and an aromatic heterocyclic group.

Such "aromatic hydrocarbon group" includes, for example, a monocyclic or condensed polycyclic aromatic hydrocarbon group having 6 to 14 carbon atoms. Specifically, such aromatic hydrocarbon group includes C_{6-14} aryl such as phenyl, 1-naphthyl, 2-naphthyl, indenyl and anthryl. Among others, phenyl, 1-naphthyl and 2-naphthyl are preferable.

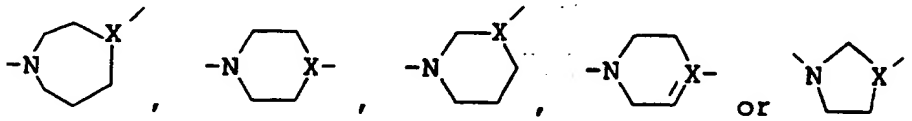
ring which may be substituted" represented by ring A above, the number of such substituents being 1 to 5, preferably 1 to 3. Provided that 2 or more substituents are present, they may be identical or not. Among others, preferred is halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenat d 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino, di-C_{7-16} aralkylamino, etc. More preferred is halogen, C_{1-3} alkylenedioxy (preferably methylenedioxy), an optionally halogenated C_{1-6} alkyl, an optionally halogenated C_{1-6} alkoxy, cyano, hydroxy etc.

Ar^1 is preferably a phenyl or 5- or 6-membered aromatic heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, optionally halogeneated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy. More preferred is a phenyl or pyridyl group which may be substituted by 1 to 3 halogen atoms (e.g., chlorine, fluorine). Specifically, phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl or 4-pyridyl is exemplified.

Ar^2 is preferably a phenyl or 5- or 6-membered aromatic heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-

wherein Za represents a divalent group represented by the formula: $-CH_2-CH_2-$, $-CH_2-O-$, $-CO-O-$, $-CH_2-NR^{4a}-$, $-CH=N-$ or $-N=CH-$ wherein R^{4a} represents a C_{1-6} alkyl or a C_{1-6} alkyl-carbonyl; n represents an integer from 0 to 2,

ring C is a 5- to 7-membered nitrogen-containing heterocyclic ring represented by the formula:



wherein X represents a carbon atom or a nitrogen atom, which may be substituted by 1 to 3 substituents selected from the group consisting of cyano, an optionally halogenated C_{1-6} alkyl, an optionally halogenated C_{1-6} alkoxy, an optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxy, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl and C_{1-6} alkyl-carbonylamino,

Y is a bond or a methylene,

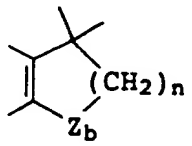
Ar^1 is a phenyl or pyridyl group which may be substituted by 1 to 3 halogen atoms,

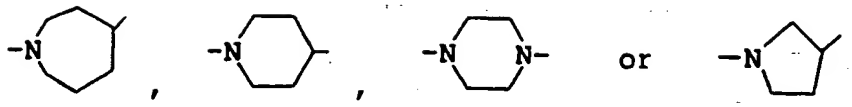
Ar^2 is a phenyl or pyridyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, an optionally halogenated C_{1-6} alkyl and an optionally halogenated C_{1-6} alkoxy, and

m is 1 or 2.

More preference is given to those compounds wherein ring A is a benzene ring,

ring B is a ring represented by the formula:





which may be substituted by the substituents selected from the group consisting of a cyano, a hydroxy and a C_{1-6} alkyl-carbonyl,

Y is a bond or a methylene,

Ar^1 is a phenyl or pyridyl group which may be substituted by a halogen, preferably a phenyl,

Ar^2 is a phenyl which may be substituted by a halogen atom, an optionally halogenated C_{1-6} alkyl or a C_{1-6} alkoxy, and

m is 2.

Preferable examples of compound (I) include
4-phenyl-4-[2-(4-phenylpiperidino)ethyl]isochroman,
4-phenyl-4-[2-(4-hydroxy-4-phenylpiperidino]ethyl)isochroman,
4-{2-[4-(m-fluorophenyl)piperidino]ethyl}-4-phenylisochroman,
4-{2-[4-(o-methoxyphenyl)piperazin-1-yl]ethyl}-4-phenylisochroman,
1,3-dihydro-1-ethyl-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one,
1,3-dihydro-1-ethyl-3-(2-(4-hydroxy-4-phenylpiperidino)ethyl)-3-phenyl-2H-indol-2-one,
2-methyl-3-oxo-4-phenyl-4-(2-(4-phenylpiperidino)ethyl)-1,2,3,4-tetrahydroisoquinoline and
salts thereof.

Of the compounds represented by formula (I), compound (Ia) is a new compound.

"Ring A", "ring C", "X", "Y", "Ar^1", "Ar^2" and "m" in formula (Ia) above are defined as the same as "ring A", "ring C", "X", "Y", "Ar^1", "Ar^2" and "m" described in detail with respect to formula (I) above.

alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl which may be substituted, C_{6-10} aryloxy which may be substituted, 5- to 10-membered aromatic heterocyclic group which may be substituted, acyloxy, phthalimido which may be substituted, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkyl. More preferred is a C_{1-6} alkyl or C_{7-16} aralkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, cyano, optionally halogenated C_{3-6} cycloalkyl, epoxyethyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyloxy and phthalimido.

The "acyl" represented by R^6 or R^{6a} is identical to the "acyl" described in detail as the "substituent" for the "benzene ring which may be substituted" represented by ring A above. Among others, preferred is C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{1-6} alkylsulfonyl and C_{6-10} arylsulfonyl. More preferred is C_{1-6} alkyl-carbonyl.

The "amino which may be substituted" represented by R^6 or R^{6a} is exemplified by (i) an amino which may be substituted by 1 or 2 "hydrocarbon group which may be substituted" or "heterocyclic group which may be substituted, and (ii) a 3- to 7-membered saturated cyclic amino.

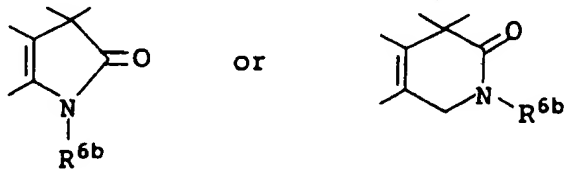
The above "hydrocarbon group which may be substituted", "heterocyclic group which may be substituted" and "3- to 7-membered saturated cyclic amino" are identical to the "hydrocarbon group which may be substituted", "heterocyclic group which may be substituted" and "3- to 7-membered saturated cyclic amino" described in detail with respect to the "substituent" for the "benzene ring which may be substituted" represented by ring A above.

mono- or di-C_{7-16} aralkylamino or a 3- to 7-membered saturated cyclic amino.

The "substituent" for the "5- to 7-membered carbocyclic or heterocyclic ring which may be substituted" represented by ring B' is exemplified by the same substituents as those that may be present in the "benzen ring which may be substituted" represented by ring A above, the number of such substituents being 1 to 3. Provided that 2 or more substituents are present, they may be identical or not.

Of the compounds represented by formula (Ia) above, preference is given to those compounds wherein ring A is a benzene ring which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen atom, C_{1-3} alkylenedioxy, nitro, cyano, an optionally halogenated C_{1-6} alkyl, an optionally halogenated C_{1-6} alkoxy, an optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxy, carbamoyl and C_{1-6} alkoxycarbonyl,

ring B' is a ring represented by the formula:



wherein R^{6b} represents (i) a hydrogen atom,
(ii) a C_{1-6} alkyl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen atom, C_{1-3} alkylenedioxy, nitro, cyano, an optionally halogenated C_{1-6} alkyl, an optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, an optionally halogenated C_{1-6} alkoxy, an optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6}

C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl and C_{1-6} alkyl-carbonylamino,

Y is a bond or a methylene,

Ar^1 is a phenyl or pyridyl group which may be substituted by 1 to 3 halogen atoms,

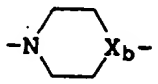
Ar^2 is a phenyl or pyridyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, an optionally halogenated C_{1-6} alkyl and an optionally halogenated C_{1-6} alkoxy, and

m is 1 or 2.

Of these compounds, more preference is given to those compounds wherein ring A is a benzene ring,

R^{6b} is (i) a hydrogen atom, (ii) a C_{1-6} alkyl or C_{7-16} aralkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of cyano, C_{3-6} cycloalkyl, epoxyethyl, an optionally halogenated C_{1-6} alkoxy, amino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, C_{1-6} alkoxy-carbonyl, C_{1-6} alkyl-carbonyloxy and phthalimido, (iii) a C_{1-6} alkyl-carbonyl, or (iv) a di-C_{1-6} alkylamino,

ring C is a 6-membered nitrogen-containing heterocyclic ring containing at least one nitrogen atom which may be oxidized, represented by the formula:



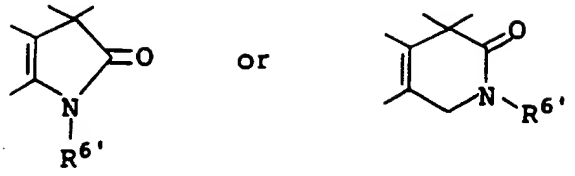
wherein Xb represents (i) a nitrogen atom or (ii) a group represented by the formula: $>C(R^{5b})-$ wherein R^{5b} represents a hydrogen atom, an optionally halogenated C_{1-6} alkyl or a hydroxy,

Y is a bond,

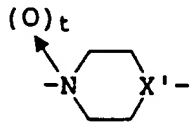
Ar^1 is a phenyl,

Ar^2 is a phenyl which may be substituted by an optionally halogenated C_{1-6} alkoxy, and

m is 2.



wherein $R^{6'}$ is (i) a hydrogen atom,
(ii) a C_{1-6} alkyl, C_{2-6} alkenyl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, cyano, 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, hydroxy, amino, mono- or di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, C_{1-6} alkoxy-carbonyl, C_{1-6} alkyl-carbonyloxy, phthalimido and C_{1-6} alkoxy-C_{1-6} alkoxy,
(iii) a C_{1-6} alkyl-carbonyl, or
(iv) a mono- or di-C_{1-6} alkylamino, a mono- or di-C_{7-16} aralkylamino or a 3- to 7-membered saturated cyclic amino,
ring C is a ring of the formula:



wherein X' is (i) a nitrogen atom or (ii) a group of the formula: $>C(R^{5'})-$
wherein $R^{5'}$ is a hydrogen atom, cyano, hydroxy or C_{1-6} alkyl-carbonyl, and t is 0 or 1,
Y is a bond,
Ar^1 is a phenyl,
Ar^2 is a phenyl or pyridyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, nitro, cyano, optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono- or di-C_{1-6} alkylamino, mono-C_{1-6} alkyl-carbonylamino, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, and
m is 2.

salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid etc. Preferable salts with organic acids include, for example, salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid etc. Preferable salts with basic amino acids include, for example, salts with arginine, lysine, ornithine etc. Preferable salts with acidic amino acids include, for example, salts with aspartic acid, glutamic acid etc.

Of these salts, pharmaceutically acceptable salts are preferred. Examples of such salts include inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt) and alkaline earth metal salts (e.g., calcium salt, magnesium salt, barium salt), and ammonium salt when compound (I) or (Ia) has an acidic functional group therein; and inorganic salts such as hydrochloride, sulfate, phosphate and hydrobromide, or organic salts such as acetate, maleate, fumarate, succinate, methanesulfonate, p-toluenesulfonate, citrate and tartrate when compound (I) or (Ia) has a basic functional group therein.

A production method for compound (I), which includes compound (Ia) is described below.

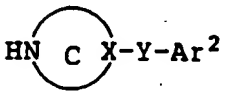
Compound (I) can be obtained by commonly known methods, e.g., those described in JP-A-8-1154542, JP-A-8-3045, EP-679642, JP-A-8-12650, USP 3,880,885, USP 4,247,553, USP 2,759,936, USP 3,314,954, USP 3,595,866, USP 2,759,935, J. Am. Chem. Soc. Vol. 84, p. 4574 (1962), J. Am. Chem. Soc. Vol. 87, p. 3451 (1965) etc., or methods analogous thereto, and also by, for example, the methods shown by the following schemes.

The compounds shown in the following schemes include their salts, exemplified by the same salts as those of compound (I).

Process 2

Compound (III) is subjected to a conventional alkylation to yield compound (I).

The alkylation can be accomplished by reacting compound (III) with 1 to 5 equivalents (preferably 1 to 3 equivalents) of the compound represented by the formula:



wherein each symbol has the same definition as those shown above, or its salt in an inert solvent at room temperature to 200°C, preferably room temperature to 50°C, for 0.5 hours to one day. Although 1 to 3 equivalents of base is normally added, it is not always essential.

Useful inert solvents include alcohol solvents (e.g., methanol, ethanol, tert-butanol), ether solvents (e.g., ethyl ether, tetrahydrofuran, dioxane), halogen solvents (e.g., dichloromethane), aromatic solvents (e.g., benzene, toluene, xylene), nitrile solvents (e.g., acetonitrile, propionitrile), amide solvents (e.g., N,N-dimethylformamide (DMF)), ketone solvents (e.g., acetone, methyl ethyl ketone) and sulfoxide solvents (e.g., dimethyl sulfoxide); these solvents may be used singly or in combination of 2 or more kinds. Of these solvents, acetonitrile, DMF, acetone, ethanol etc. are preferred.

The base is exemplified by 1) strong bases such as alkali metal or alkaline earth metal hydrides (e.g., lithium hydride, sodium hydride, potassium hydride, calcium hydride), alkali metal or alkaline earth metal amides (e.g., lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethylsilazide, sodium hexamethylsilazide, potassium hexamethylsilazide), and alkali m tal or alkaline earth metal lower alkoxides (e.g., sodium methoxide, sodium

(2) the above compound or its salt is reacted with 1 to 2 equivalents of the compound represented by the formula:

$$L^a\text{-}Y\text{-}Ar^2$$

wherein L^a represents a leaving group, and other symbols have the same definition as those shown above, or its salt.

The "amino protective group" represented by T is as same as "amino protective group" described later.

The "leaving group" represented by L^a is identical to "leaving group" of L above.

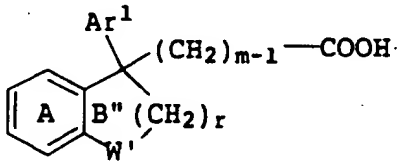
The deprotection reaction in above (1) can be accomplished by known methods. For example, where T is formyl, hydrolysis can be utilized. The alkali hydrolysis or the acid hydrolysis can be used for the hydrolysis and acid hydrolysis is preferable. As a typical procedure of the acid hydrolysis, the ligand is stirred under heating with an excess mineral acid (e.g. hydrochloric acid, sulfuric acid, phosphoric acid, etc.) in an inert solvent at room temperature (0 to 30°C) to 120°C for 0.5 to 18 hours.

The inert solvent includes water and acetic acid. These solvents can be used singly or in combination of these two kinds. Typically, the reaction can be done by reacting the ligand with excess hydrochloric acid in either water or acetic acid at a temperature of 80 to 120°C.

The above-described reaction (2) can be achieved by the similar manner as an alkylation referred to above. Where Y is a bond, the following reaction condition may be applicable. Preferable solvents includes amide solvents (e.g., N,N-dimethylformamide (DMF)), ketone solvents (e.g., acetone, methylethylketone) and sulfoxide solvents (e.g., dimethylsulfoxide). These solvents can be used singly or in combination of two or more kinds. Preferred solvents are DMF, acetone and ethanol. Preferred temperature is 50 to 200°C. Where the solvent is DMF, preferable temperature

W' represents a divalent group of the formula: $-CH_2-CH_2-$, $-CH=CH-$, $-CO-O-$, $-CO-NR^6-$, $-NR^6-CO-$, $-N=CH-$, $-CH_2-S(O)_p-$, $-N=N-$, $-NR^6-SO_2-$, $-SO_2-NR^6-$, $-NR^6-NR^{6a}-$, $-CH_2-O-$, $-CH_2-NR^6-$, $-NR^6-CH_2-$, $-CH=N-$, $-CH_2-NR^6-CO-$ or $-CO-NR^6-CO-$ wherein R^6 and R^{6a} each represents a hydrogen atom, an optionally substituted hydrocarbon group, acyl or an optionally substituted amino, and p represents an integer of 0 to 2; and the other symbols have the same definitions as those shown above, and or a salt thereof is a new compound. The "optionally substituted 5- to 7-membered carbocyclic or heterocyclic ring" for B" ring is identical to the "optionally substituted 5- to 7-membered carbocyclic or heterocyclic ring" for B' ring above.

The above optical isomer and a salt thereof can be produced by commonly methods, for example, the method which comprises forming a salt of a racemate of the formula:



wherein all symbols are as defined above, with an optical active amine, and then subjecting the resultant salt to fractional recrystallization.

The "optical active amine" includes, for example, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, (1S,2S)-(+)-2-amino-1-phenyl-1,3-propanediol.

Process 4

The amide bond in compound (V) is reduced to yield compound (I).

The reduction is carried out using a metal hydride. Specifically, compound (V) and a metal hydride (e.g., lithium aluminum hydride, sodium borohydride, lithium borohydride, sodium cyanoborohydride, diborane, dibutyl

Process 5

Compound (VI) is subjected to a commonly known oxidation to yield compound (VII).

Compound (VI) can be produced by the method described in EP-679642 or a method analogous thereto.

The oxidation normally employs an oxidizing agent such as ruthenium oxide, chromic acid or a analog thereof, or a permanganate. It is preferable that ruthenium oxide be used stoichiometrically and catalytically. The oxidation is carried out by the method described in the Journal of Organic Chemistry, Vol. 46, p. 3936 (1981), for example. Specifically, compound (VI), a catalytic amount of ruthenium trichloride hydrate, and excess sodium periodate are reacted at nearly room temperature in a mixed solvent system consisting of acetonitrile, carbon tetrachloride and water for 1 to 20 hours.

Compound (VII) as obtained by the above-described oxidation is converted to compound (I) by the same method as process 2 in the above-described scheme 1.

When compound (I) is a tetrahydronaphthalene, the desired product may, for example, be produced from compound (II) or (IV) as obtained by the following scheme 3 via the same reaction process as the process in the above-described scheme 1.

The cyclization is carried out in an acidic environment. For example, compound (IX) is reacted in an inert solvent (e.g., alcohol solvents, ether solvents, halogen solvents, aromatic solvents), in an organic acid (e.g., carboxylic acids such as acetic acid and formic acid, and sulfonic acids such as methanesulfonic acid, trifluoromethanesulfonic acid and benzenesulfonic acid), or in a mixed system consisting of 2 or more thereof, in the presence of a catalytic to excess amount of acid catalyst added as necessary, at room temperature to 120°C (preferably room temperature to 50°C) for 1 to 24 hours. Preferably, compound (IX) is reacted in a halogen solvent, such as dichloromethane, in the presence of a catalytic to excess amount of Lewis acid (preferably 1 to 2 equivalents of boron trifluoride-diethyl ether complex) at room temperature for 1 to 6 hours.

Process 8

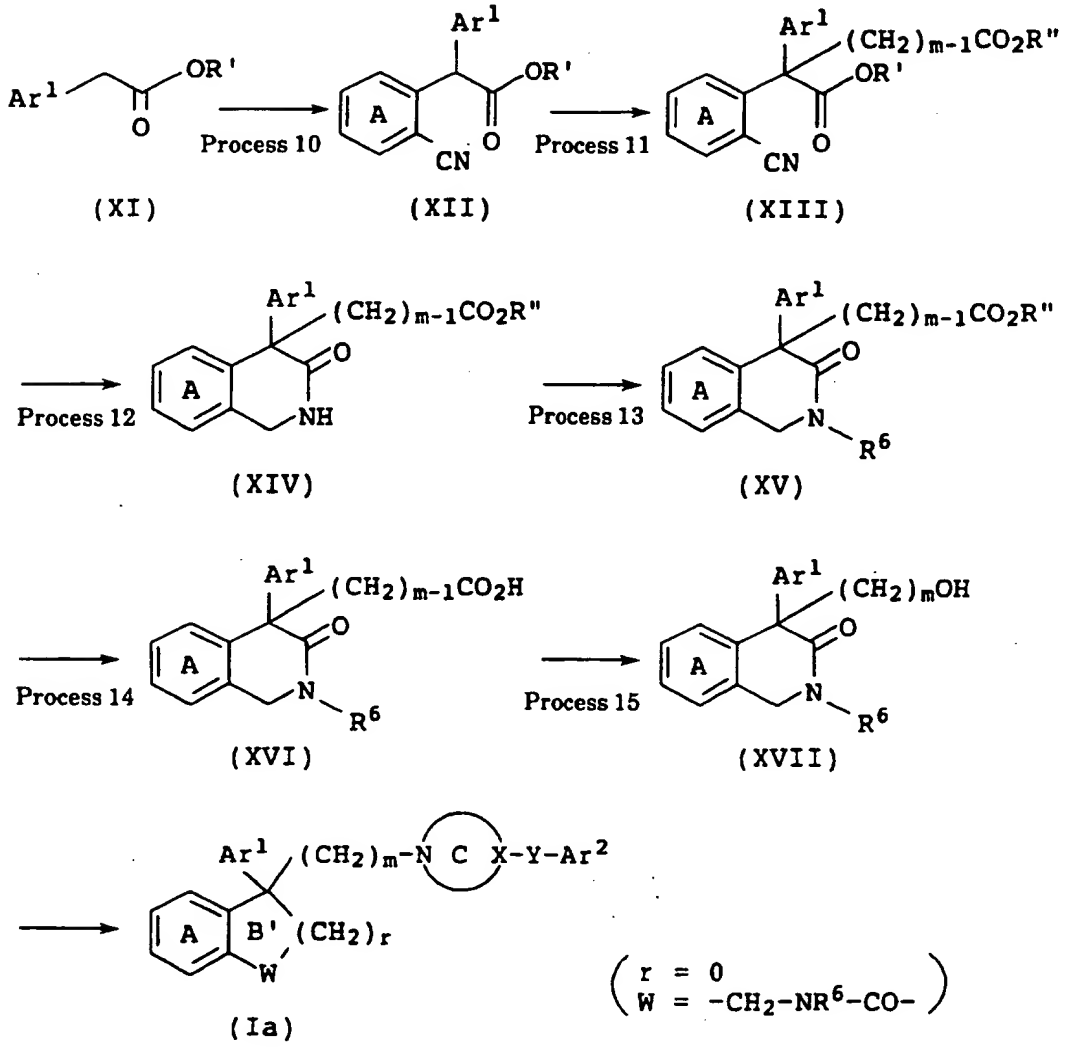
Compound (X) is subjected to reduction to yield compound (II).

The reduction is carried out using a metal hydride. For example, compound (X) is reacted with a metal hydride (e.g., lithium aluminum hydride, sodium borohydride, lithium borohydride, sodium cyanoborohydride, diborane, dibutyl aluminum hydride), a metal (e.g., zinc, iron, sodium, potassium), or the like, in an inert solvent.

Inert solvents include ether solvents (e.g., ethyl ether, tetrahydrofuran, dioxane), alcohol solvents (e.g., methanol, ethanol, tert-butanol), aromatic solvents (e.g., benzene, toluene, xylene) and hydrocarbon solvents (e.g., hexane). Such metal hydrides preferably include lithium aluminum hydride. The amount of metal hydride used is normally about 1 to 20 equivalents, preferably 2 to 6 equivalents, per mol of compound (X). Reaction temperature is -70 to 100°C. Although reaction temperature varies depending on the reducing agent used, it is preferably 0 to 50°C when lithium aluminum hydride is used.

obtained by a commonly known method or the following scheme 4 via the same reaction process as the process in the above-described scheme 1.

Scheme 4



wherein each of R' and R" represents a lower alkyl; the other symbols have the same definitions as those shown above.

The "lower alkyl" represented by R' or R" is identical to the "lower alkyl" represented by R above.

Process 11

Compound (XII) is subjected to a commonly known alkylation to yield compound (XIII).

The alkylation is carried out by stirring compound (XII), 1 to 3 equivalents of a compound represented by the formula: $L-(CH_2)_{m-1}-COOR''$ wherein the symbols have the same definitions as those shown above, and 1 to 3 equivalents of base in an inert solvent at -50 to 50°C (preferably 0°C) for 0.5 to 8 hours.

The base is exemplified by the strong bases, inorganic bases, organic bases etc. described in detail with respect to the above-described process 2. Among others, sodium hydride, potassium hydride, sodium amide, lithium diisopropylamide, potassium tert-butoxide, potassium carbonate etc. are preferred.

The inert solvents include, for example, halogen solvents (e.g., dichloromethane), ether solvents (e.g., ethyl ether, tetrahydrofuran, dioxane), aromatic solvents (e.g., benzene, toluene, xylene), nitrile solvents (e.g., acetonitrile, propionitrile), amide solvents (e.g., DMF) and sulfoxide solvents (e.g., dimethyl sulfoxide); these solvents may be used singly or in combination of 2 or more kinds. Of these solvents, tetrahydrofuran, DMF, dimethyl sulfoxide etc. are preferred.

Process 12

Compound (XIII) is subjected to a commonly known catalytic reduction to yield compound (XIV).

The reduction is carried out by reacting compound (XIII) with a catalytic amount of metal catalyst in an inert solvent at room temperature to 100°C (preferably 50 to 80°C) under a hydrogen pressure of 1 to 100 atm (preferably 3 to 10 atm) for 1 to 48 hours. Metal catalysts include, for example, Raney nickel, Raney cobalt, platinum oxide, metallic palladium and palladium-carbon.

The inert solvents include, for example, alcohol solvents (e.g., methanol, ethanol, tert-butanol), ether

acetonitrile, propionitrile), amid solvents (e.g., DMF) and sulfoxide solvents (e.g., dimethyl sulfoxide); these solvents may be used singly or in combination of 2 or more kinds. Of these solvents, tetrahydrofuran, DMF, dimethyl sulfoxide etc. are preferred.

Process 14

Compound (XV) is subjected to a hydrolysis to yield compound (XVI).

The hydrolysis may be carried out in the same manner as in the above-described process 9.

Process 15

Compound (XVI) is subjected to a commonly known reduction to yield compound (XVII).

The reduction is carried out by reacting compound (XVI) and about 1 to 5 equivalents (preferably 1 to 2 equivalents) of metal hydride in an inert solvent at -70 to 100°C (preferably 20 to 60°C) for 1 to 24 hours.

The metal hydride is exemplified by lithium aluminum hydride, sodium borohydride, diborane and diisobutyl aluminum hydride. Among others diborane is preferred. The inert solvents include, for example, ether solvents (e.g., ethyl ether, tetrahydrofuran, dioxane) and aromatic solvents (e.g., benzene, toluene, xylene); these solvents may be used singly or in combination of 2 or more kinds. Of these solvents, tetrahydrofuran etc. are preferred.

Compound (XVII) thus obtained is subjected to the same reaction process as the process for preparing compound (I) from compound (II) in the above-described scheme 1 to yield compound (I) or (Ia), which has an isoquinolone structure.

When the starting compound involved in each reaction described above has amino, carboxy or hydroxy as a substituent, the group may be protected by a protecting group commonly used in peptide chemistry and other fields; the desired compound can be obtained by removing the protecting group if necessary after r action.

using acid, base, ultraviolet light, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate etc., and reduction.

Compound (I) can be isolated and purified by known means such as solvent extraction, liquid nature conversion, re-dissolution, crystallization, recrystallization and chromatography. Also, the starting compounds and synthetic intermediates for compound (I) or a salt thereof can be isolated and purified by the same known means as those mentioned above, but may be used as the starting material for the next process as a reaction mixture as is without isolation.

Also, compounds (I) and (Ia) may be hydrates or non-hydrates.

When compound (I) or (Ia) contains an optical isomer, a stereoisomer, a position isomer or a rotational isomer, these isomers are also included in the scope of compound (I) or (Ia), and each can be obtained as a single product by commonly known means of synthesis and separation. For example, when an optical isomer is present in compound (I) or (Ia), the optical isomer separated from the compound is also included in the scope of compound (I) or (Ia).

An optical isomer can be produced by commonly known methods. Specifically, an optical isomer is obtained by using an optical active synthesis intermediate or by optically resolving the final racemate by a conventional method.

Useful methods of optical resolution include commonly known methods such as the fractional recrystallization method, the chiral column method and the diastereomer method.

1) Fractional recrystallization method

A racemate is formed a salt thereof with an optically active compound [e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-malic acid,

(e.g., MPTA [α-methoxy-α-(trifluoromethyl)phenylacetic acid], (-)-methoxyacetic acid) etc. to a condensation. On the other hand, when compound (I) or (Ia) has a carboxylic acid group, an ester or amide diastereomer, respectively, is obtained by subjecting the compound and an optically active amine or alcohol reagent to a condensation. The diastereomer thus separated is converted to an optical isomer of the original compound by an acid hydrolysis or basic hydrolysis.

Compounds (I) and (Ia) are low in toxicity. For example, in an acute toxicity study using rats, no death was observed when the compound obtained in Reference Example 4-1 below was orally administered at 100 mg/kg. Compounds (I) and (Ia) have a good activity of controlling micturition and can be safely used at low doses as a pharmaceutical composition for controlling micturition in mammals such as humans to suppress micturition reflex and increase the bladder's volume. For example, it can be used to suppress the urge incontinence, or as a composition for the prophylaxis or treatment of lower urinary tract dysfunctions such as pollakiuria and urinary incontinence (stress incontinence, urge incontinence, reflex incontinence, overflow incontinence, total incontinence, asymptomatic incontinence). Compounds (I) and (Ia) are preferably used as a composition for the prophylaxis or treatment of pollakiuria and/or urinary incontinence.

Also, compounds (I) and (Ia) possess analgesic activity, and can also be used as a pharmaceutical composition for the prophylaxis or treatment of pain associated with bone diseases (e.g., arthritis, rheumatism, osteoporosis), chronic pain associated with cancer etc., lumbago, postoperative pain, neuralgia, pain associated with inflammatory diseases, tooth extraction pain, tooth pain, pain due to burns and traumas, and diseases such as neuropathy (e.g., anxiety, depression, psychosis) and somnipathy, in mammals such as humans.

Excipients include, for example, lactose, saccharose, D-mannitol, starch, corn starch, crystalline cellulose and light silicic anhydride.

Lubricants include, for example, magnesium stearate, calcium stearate, talc and colloidal silica.

Binders include, for example, crystalline cellulose, saccharose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, starch, sucrose, gelatin, methyl cellulose and carboxymethyl cellulose sodium.

Disintegrants include, for example, starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl starch sodium and L-hydroxypropyl cellulose.

Solvents include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil and corn oil.

Dissolution aids include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, tris-aminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Suspending agents include, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Isotonizing agents include, for example, glucose, D-sorbitol, sodium chloride, glycerol and D-mannitol.

Buffers include, for example, buffer solutions of phosphates, acetates, carbonates and citrates.

Soothing agents include, for example, benzyl alcohol.

Preservatives include, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Examples

Reference Example 1-1

2,2-Diphenyl-1,4-butanediol

α,α-Diphenyl-γ-butyrolactone (7 g) was dissolved in anhydrous THF (80 ml) and lithium aluminum hydride (1 g) was added under ice cooling conditions, followed by stirring for 3 hours. To the reaction mixture was added dropwise a saturated aqueous solution of Rochelle salt under ice cooling conditions to precipitate inorganic material such as aluminum hydroxide. The supernatant was separated by decantation, dried, and concentrated under reduced pressure. The residue was recrystallized from isopropyl ether to yield the title compound (7 g).
^{1}H-NMR ($CDCl_3$) δ: 2.54 (2H, t), 3.61 (2H, t), 4.21 (2H, s), 7.16-7.45 (10H, m)

Reference Example 1-2

2,2-Diphenyl-1,5-pentanediol

Ethyl 4-cyano-4,4-diphenylbutyrate (24 g) was dissolved in THF (120 ml) and added dropwise to a suspension of lithium aluminum hydride (4.2 g) in THF (200 ml) under ice cooling conditions. After being stirred for 2 hours under ice cooling conditions, 2 N hydrochloric acid (200 ml) was added, followed by stirring under heating at 60°C for 2 hours. To the reaction mixture was added ethyl acetate (400 ml) and the organic layer was separated, dried, and concentrated under reduced pressure. The residue was dissolved in THF (200 ml) and lithium aluminum hydride (4 g) was added under ice cooling conditions. After being stirred for 2 hours, a saturated aqueous solution of Rochelle salt was added dropwise to the reaction mixture under ice cooling conditions to precipitate inorganic material such as aluminum hydroxide. The supernatant was separated by decantation, dried, and concentrated under reduc d pressure. The residue was

4-(2-Hydroxyethyl)-4-phenylisochroman (1 g) was dissolved in methylene chloride (20 ml) followed by addition of tosyl chloride (0.85 g) and triethylamine (1.5 ml) under ice cooling conditions. After being stirred at room temperature for 2 hours. The mixture was acidified by the addition of 2 N hydrochloric acid and extracted with isopropyl ether. The organic layer was washed with water, dried, and concentrated under reduced pressure. The residue was dissolved in acetone (50 ml) followed by addition of sodium iodide (2 g) was added, followed by stirring under heating at 50°C for 24 hours. After the mixture was cooled, water was added, followed by extraction with isopropyl ether. The organic layer was washed with water, dried, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with isopropyl ether to yield the title compound.
^{1}H-NMR ($CDCl_3$) δ: 2.76-3.08 (3H, m), 3.20-3.39 (1H, m), 3.89 (2H, q), 4.87 (2H, s), 6.90 (1H, d), 7.01-7.38 (8H, m)

Reference Example 3-2
4-(3-Iodopropyl)-4-phenylisochroman

The title compound was obtained in the same manner as in Reference Example 3-1.
Melting point: 39 - 40°C
^{1}H-NMR ($CDCl_3$) δ: 1.50-2.00 (2H, m), 2.29 (2H, m), 3.16 (2H, dt), 3.90 (2H, s), 4.88 (2H, s), 6.90-7.30 (9H, m)

Reference Example 4-1
4-Phenyl-4-[2-(4-phenylpiperidino)ethyl]isochroman hydrochloride

To a solution of 4-phenyl-4-(2-iodoethyl)isochroman (2.6 g) in acetonitrile (50 ml) were added 4-phenylpiperidine (1.39 g) and potassium carbonate (1.56 g). The mixture was stirred under heating at 60°C overnight. Th insoluble material in the reaction mixture was filtered off and the filtrate was concentrated to dryness. The

^{1}H-NMR ($CDCl_3$) δ: 1.90-2.22 (4H, m), 2.25-2.66 (6H, m), 2.96-3.11 (2H, m), 3.94 (2H, s), 4.88 (2H, s), 6.94-7.53 (14H, m)

Reference Example Compound 4-4: 4-{2-[4-(o-Fluorophenyl)piperidino]ethyl}-4-phenylisochroman hydrochloride

Melting point: 174 - 176°C

Reference Example Compound 4-5: 4-{2-[4-(m-Fluorophenyl)piperidino]ethyl}-4-phenylisochroman hydrochloride

Melting point: 232 - 236°C

Reference Example Compound 4-6: 4-{2-[4-(p-Fluorophenyl)piperidino]ethyl}-4-phenylisochroman hydrochloride

Melting point: 245-250°C

Reference Example Compound 4-7: 4-Phenyl-4-[2-(4-phenylpiperazin-1-yl)ethyl]isochroman dihydrochloride

Melting point : 238 - 240°C

Elemental analysis: (for $C_{27}H_{30}N_2O \cdot 2HCl$)

Calculated : C, 68.78; H, 6.84; N, 5.94

Found : C, 68.53; H, 6.98; N, 5.81

Reference Example Compound 4-8: 4-{2-[4-(o-Methoxyphenyl)piperazin-1-yl)ethyl}-4-phenylisochroman dihydrochloride

Melting point: 158 - 161°C

Reference Example Compound 4-9: 4-{2-[4-(p-Chlorophenyl)-4-hydroxypiperidino]ethyl}-4-phenylisochroman hydrochloride

^{1}H-NMR ($CDCl_3$) δ: 1.16-1.85 (3H, m), 2.00-2.20 (2H, m), 2.22-2.62 (6H, m), 2.73-2.90 (2H, m), 3.94 (2H, s), 4.87 (2H, s), 6.95-7.35 (11H, m), 7.43 (2H, d)

Reference Example Compound 4-10: 4-{2-[4-(p-Chlorophenyl)piperidino]ethyl}-4-phenylisochroman hydrochloride

1-(2-Iodoethyl)-1-phenyl-1,2,3,4-tetrahydronaphthalene

To a solution of triphenylphosphine (0.95 g) in methylene chloride (15 ml) were added imidazole (0.25 g) and iodine (0.92 g) sequentially. A solution of 1-(2-hydroxyethyl)-1-phenyl-1,2,3,4-tetrahydronaphthalene (0.7 g) in methylene chloride (5 ml) was added and the mixture was stirred at room temperature in an argon stream for 3 hours. The reaction mixture was washed with a solution of sodium thiosulfate and concentrated to dryness. The residue obtained was purified by silica gel column chromatography to yield the title compound (0.70 g).
Melting point: 82 - 83°C

Reference Example 11

1-[2-(4-Phenylpiperidino)ethyl]-1-phenyl-1,2,3,4-tetrahydronaphthalene hydrochloride (Reference Example Compound 11)

To a solution of 1-(2-iodoethyl)-1-phenyl-1,2,3,4-tetrahydronaphthalene (0.14 g) and 4-phenylpiperidine (75 mg) in DMF (3 ml) was added potassium carbonate (80 mg) and the mixture was stirred under heating at 65°C for 1 day. After the reaction mixture was concentrated to dryness, the residue was dissolved in ethyl acetate. The insoluble material was filtered off and the filtrate was concentrated to dryness. The residue obtained was purified by silica gel column chromatography and treated with a 4N solution of hydrogen chloride/ethyl acetate to yield the title compound (0.14 g).
^{1}H-NMR ($CDCl_3$) δ: 1.44-2.30 (11H, m), 2.30-2.56 (4H, m), 2.73-2.86 (2H, m), 3.00-3.15 (2H, m), 7.02-7.35 (14H, m)

Reference Example 12

1-Oxo-4-phenyl-4-[2-(4-phenylpiperidino)ethyl]isochroman hydrochloride (Reference Example Compound 12)

4-(2-Iodoethyl)-4-phenylisochroman (1.8 g) was dissolved in a solvent mixture of acetonitrile (15 ml),

Reference Example Compound 13-2: 6,7-Dimethoxy-4-(2-(4-hydroxy-4-phenylpiperidino)ethyl)-4-phenylisochroman hydrochloride
Melting point: 238 - 241°C

Reference Example Compound 13-3: 4-(p-Fluorophenyl)-4-(2-(4-phenylpiperidino)ethyl)isochroman hydrochloride
Melting point: 134 - 137°C

Reference Example Compound 13-4: 4-(p-Fluorophenyl)-4-(2-(4-(o-methoxyphenyl)piperazin-1-yl)ethyl)isochroman dihydrochloride
Melting point: 152 - 157°C

Reference Example Compound 13-5: 4-(2-(4-Hydroxy-4-(m-trifluoromethylphenyl)piperidino)ethyl)-4-phenylisochroman hydrochloride
Melting point: 201 - 204°C

Reference Example Compound 13-6: 4-Phenyl-4-(2-(4-m-trifluoromethylphenyl)piperidino)ethyl)isochroman hydrochloride
Melting point: 199 - 203°C

Reference Example Compound 13-7: 4-(2-(4-Phenylpiperidino)ethyl)-4-(2-pyridyl)isochroman dihydrochloride
Melting point: 113 - 118°C

Reference Example Compound 13-8: 4-(2-(4-Hydroxy-4-(m-methoxyphenyl)piperidino)ethyl)-4-phenylisochroman hydrochloride
Melting point: 188 - 191°C

Reference Example Compound 13-9: 4-(2-(4-Methyl-4-phenylpiperidino)ethyl)-4-phenylisochroman hydrochloride
Melting point: 227 - 230°C

Reference Example 14

Reference Example Compound 14-1: (R)-(+)-4-Phenyl-4-(2-(4-phenylpiperidino)ethyl)isochroman (S)-mandelate

Reference Example Compound 14-2: (S)-(-)-4-Phenyl-4-(2-(4-phenylpiperidino)ethyl)isochroman (R)-mandelate

$[\alpha]_D^{20}$ = +47.2° (c = 0.490, methanol)
HPLC retention time: 11.68 minutes

Reference Example Compound 15-2:

Melting point: 222 - 226°C
$[\alpha]_D^{20}$ = -45.8° (c = 0.507, methanol)
HPLC retention time: 21.93 minutes

Reference Example 16

N-Methyl-2-bromo-2-phenylacetanilide

α-Bromophenylacetic acid (43.0 g) was added to thionyl chloride (43.6 ml), followed by refluxing for 3 hours. The excess thionyl chloride was distilled off under reduced pressure and toluene (100 ml) was added to the residue and the mixture was again concentrated under reduced pressure. The residue was added to a solution of N-methylaniline (43.5 ml) in toluene (100 ml) at room temperature, followed by stirring for 2 hours. The insoluble material was filtered off and the filtrate was washed with 1 N hydrochloric acid, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and eluted with hexane/ethyl acetate (4/1) to yield a light-yellow oily substance, which was then crystallized from hexane-isopropyl ether to yield the title compound (47.5 g).
Melting point: 58 - 60°C

Reference Example 17

1,3-Dihydro-1-methyl-3-phenyl-2H-indol-2-one

A mixture of N-methyl-2-bromo-2-phenylacetanilide (45.6 g) obtained in Reference Example 16 and anhydrous aluminum chloride (40.0 g) was stirred at 100°C for 30 minutes. The reaction mixture was poured into ice water (1,000 ml) and the resulting crystal was collected by filtration. The crystal obtained was dissolved in ethyl acetate and washed with 1 N hydrochloric acid, brine, and dried with anhydrous sodium sulfate. The solvent was

sodium chloride and dried with anhydrous sodium sulfate. The solvent and the excess starting materials were distilled off and the residue obtained was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1) to yield the title compound (176.6 g) as an oily substance.

^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.1 Hz), 4.07 (2H, q, J=7.1 Hz), 5.57 (1H, s), 6.99-7.06 (1H, m), 7.13-7.42 (7H, m), 7.89-7.97 (1H, m)

Reference Example 20

1,3-Dihydro-3-phenyl-2H-indol-2-one

Iron powder (138.3 g) was added to a solution of ethyl 2-(2-nitrophenyl)-2-phenylacetate (176.6 g) obtained in Reference Example 19 in acetic acid (1.5 L). After the reaction mixture was stirred under heating at 100°C for 1 hour, the acetic acid was distilled off under reduced pressure. To the residue, ethyl acetate was added and the insoluble material was filtered off. The insoluble material was washed with ethyl acetate and the filtrate and washings were combined and washed with 1 N hydrochloric acid. The organic layer was dried with anhydrous sodium sulfate; the solvent was distilled off. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1) to yield the title compound (84.0 g) as a crystal.

Melting point: 182-184°C (recrystallizing solvent: isopropyl ether/diethyl ether)

Reference Example 21

3-(2-Bromoethyl)-1,3-dihydro-3-phenyl-2H-indol-2-one

To a solution of 1,3-dihydro-3-phenyl-2H-indol-2-one (24.9 g) obtained in Reference Example 20 in degassed THF (200 ml) was added 90% potassium tert-butoxide (14.8 g) under an argon atmosphere, followed by stirring at room temperature for 1 hour. After the reaction mixture was

argon atmosphere, followed by heating under reflux for 14 hours. After the reaction mixture was cooled to room temperature, water was added to stop the reaction. The mixture was extracted with ethyl acetate and the extract was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried with anhydrous sodium sulfate and concentrated. The residue obtained was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1). The oily residue obtained was crystallized from hexane to yield the title compound (4.37 g) as a crystal.
Melting point: 88 - 90°C

Reference Example 24
Ethyl 2-(2-cyanophenyl)-α-phenylacetate

To a suspension of 60% sodium hydride (1.58 g), previously washed with hexane, in DMF (30 ml) was added ethyl phenylacetate (5.43 g) dropwise under ice cooling conditions. After being stirred at room temperature for 30 minutes, the mixture was again cooled with ice. Subsequently, o-fluorobenzonitrile (2.00 g) was added dropwise, followed by stirring at room temperature for 1 hour. The reaction mixture was added to ice water and made weakly acidic with concentrated hydrochloric acid. The organic layer separated was extracted with ethyl acetate and the extract was washed with water and concentrated to dryness. The residue obtained was purified by silica gel column chromatography to yield the title compound (4 g).
^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t), 4.27 (2H, q), 5.46 (1H, s), 7.28-7.40 (6H, m), 7.56 (2H, d), 7.66 (1H, d)

Reference Example 25
Diethyl 2-(2-cyanophenyl)-2-phenylsuccinate

To a suspension of 60% sodium hydride (0.54 g), previously washed with hexane, in DMF (20 ml) was added dropwis a solution of ethyl 2-(2-cyanophenyl)-α-phenylacetate (3.00 g) in DMF (10 ml) under ice cooling

extracted with ethyl acetate. Th extract was washed with water and concentrated to dryness. The residue obtained was washed with isopropyl ether to yield the title compound (0.38 g).

^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t), 3.13 (3H, s), 3.21, 4.00 (1H each, d), 3.91-4.06 (2H, m), 4.33 (2H, s), 7.00-7.10 (2H, m), 7.15-7.38 (7H, m)

Reference Example 27-2

Ethyl (2-ethyl-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate

The title compound was obtained in the same manner as in Reference Example 27-1.

^{1}H-NMR ($CDCl_3$) δ: 1.09, 1.14 (3H each, t), 3.20, 3.95 (1H each, d), 3.40-3.80 (2H, m), 3.89-4.09 (2H, m), 4.24 (2H, s), 7.00-7.10 (2H, m), 7.15-7.38 (7H, m)

Reference Example 28-1

(2-Methyl-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetic acid

To a solution of ethyl (2-methyl-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (1.38 g) in ethanol (15 ml) was added a 1 N aqueous solution of sodium hydroxide (7 ml). The mixture was stirred under heating at 60°C for 4 hours. After the ethanol was distilled off from the reaction mixture, the residue obtained was diluted with water. The dilution was acidified with 1 N hydrochloric acid and the precipitated crystal was collected by filtration, sequentially washed with water and ether to yield the title compound (1.20 g).

^{1}H-NMR ($CDCl_3$) δ: 3.00 (3H, s), 3.33, 3.56 (1H each, d), 4.33 (2H, q), 6.90-7.05 (2H, m), 7.05-7.40 (7H, m)

Reference Example 28-2

(2-Ethyl-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetic acid

Triphenylphosphine (0.28 g), imidazole (73 mg) and iodine (0.27 g) were sequentially dissolved in THF (4 ml). To the solution was added a solution of 4-(2-hydroxyethyl)-2-methyl-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinoline (0.23 g) in THF (2 ml). The mixture was stirred at room temperature in an argon stream for 3 hours. To the reaction mixture, a saturated aqueous solution of sodium thiosulfate was added and the organic layer was extracted with ethyl acetate. The extract was washed with water and concentrated to dryness. The residue obtained was purified by silica gel column chromatography to yield the title compound (70 mg).

^{1}H-NMR ($CDCl_3$) δ: 2.66-2.83 (1H, m), 2.95-3.12 (1H, m), 3.11 (3H, s), 3.18-3.43 (2H, m), 4.20 (2H, q), 6.96-7.05 (2H, m), 7.16-7.49 (7H, m)

Reference Example 30-2

2-Ethyl-4-(2-iodoethyl)-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinoline

The title compound was obtained in the same manner as in Reference Example 30-1.

^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t), 2.64-2.82 (1H, m), 2.99-3.17 (1H, m), 3.20-3.54 (3H, m), 3.61-3.80 (1H, m), 4.10 (2H, s), 6.95-7.03 (2H, m), 7.15-7.28 (4H, m), 7.29-7.50 (3H, m)

Reference Example 31

(R)-(-)-(4-Phenylisochroman-4-yl)acetic acid

(4-Phenylisochroman-4-yl)acetic acid (21.85 g) and (-)-cinchonidine (23.98 g) were mixed in ethanol, and the separated salt was collected by filtration and recrystallized from ethanol. The mother liquor obtained was concentrated, after which it was again recrystallized to yield crystals. The mother liquor obtained initially was treated with hydrochloric acid to yield a free compound. The free compound obtained and (1S,2S)-(+)-2-

organic layer was washed with brine and concentrated under reduced pressure. The residue obtained was subjected to silica gel column chromatography and eluted with hexane/ethyl acetate (3/1) to yield the title compound (0.08 g) as an oily substance.

^{1}H-NMR ($CDCl_3$) δ: 1.35-1.80 (4H, m), 2.22-2.66 (2H, m), 2.90-3.08 (1H, m), 3.19 (1H, dd), 3.49 (1H, dd), 3.68-3.96 (1H, m), 3.97-4.32 (2H, m), 4.63-4.81 (1H, m), 4.93 (2H, s), 6.96-7.45 (14H, m)

Reference Example 34

(S)-(-)-4-Phenyl-4-(2-(4-phenylpiperidino)ethyl)isochroman

To a solution of (S)-4-phenyl-1-((4-phenylisochroman-4-yl)acetyl)piperidine (0.08 g) in THF (1 ml), lithium aluminum hydride (0.01 g) was added, followed by heating under reflux for 2 hours. To the reaction mixture, water was added and the insoluble material was filtered off; the filtrate was concentrated under reduced pressure. The residue obtained was subjected to silica gel column chromatography and eluted with hexane/ethyl acetate (2/1) to yield the title compound (0.03 g). When the title compound was subjected to HPLC under the same conditions as those in Reference Example 15 above, the retention time was the same as that of Reference Example Compound 15-2.

Reference Example 35-1

N-Ethyl-2-bromo-2-phenylacetanilide

The title compound was obtained in the same manner as in Reference Example 16

Melting point: 65 - 66°C (crystallizing solvent: isopropyl ether/hexane)

Reference Example 35-2

N-Ethyl-N-(4-fluorophenyl)-2-bromo-2-phenylacetamide

To a solution of 4-fluoroaniline (19.1 ml) and triethylamine (41.8 ml) in THF (200 ml) was added dropwise

Melting point: 95 - 96°C (crystallizing solvent: isopropyl ether/hexane)

Reference Example 36-2: 1-Ethyl-5-fluoro-1,3-dihydro-3-phenyl-2H-indol-2-one

Melting point: 108 - 110°C (crystallizing solvent: ethyl acetate/hexane)

Reference Example 37

Compounds in Reference Examples 37-1 and 37-2 below were obtained in the same manner as in Reference Example 18.

Reference Example 37-1: 3-(2-Bromoethyl)-1-ethyl-1,3-dihydro-3-phenyl-2H-indol-2-one

Melting point: 55 - 56°C (crystallizing solvent: isopropyl ether/hexane)

Reference Example 37-2: 3-(2-Bromoethyl)-1-ethyl-5-fluoro-1,3-dihydro-3-phenyl-2H-indol-2-one

Melting point: 111 - 112°C (crystallizing solvent: isopropyl ether/hexane)

Reference Example 38

Compounds in the following Reference Examples 38-1 through 38-3 were obtained in the same manner as in Reference Example 22.

Reference Example 38-1: 1,3-Dihydro-3-phenyl-1-piperidino-2H-indol-2-one

Melting point: 123 - 125°C (crystallizing solvent: isopropyl alcohol)

Reference Example 38-2: 1-(Diethylamino)-1,3-dihydro-3-phenyl-2H-indol-2-one

Melting point: 71 - 74°C (crystallizing solvent: ethyl acetate/hexane)

Reference Example 38-3: 1,3-Dihydro-1-bis(phenylmethyl)amino-3-phenyl-2H-indol-2-one

^{1}H-NMR ($CDCl_3$) δ: 4.21 (1H, d, J=12.5 Hz), 4.37 (1H, s), 4.43 (1H, d, J=12.5 Hz), 4.56 (1H, d, J=12.5Hz), 4.58 (1H,

(2H, m), 3.55-3.73 (1H, m), 3.78-3.96 (1H, m), 6.92 (1H, d, J=7.7 Hz), 7.10 (1H, t, J=7.4 Hz), 7.20-7.38 (7H, m), 7.96 (1H, s)

Reference Example 41

1-Ethyl-1,3-dihydro-3-phenyl-3-(2-(piperazin-1-yl)ethyl)-2H-indol-2-one

A mixture of 1-ethyl-3-(2-(4-formylpiperazin-1-yl)ethyl)-1,3-dihydro-3-phenyl-2H-indol-2-one (17.9 g) obtained in Reference Example 40 and 3 N hydrochloric acid (270 ml) was refluxed with stirring for 2 hours. The reaction mixture was cooled to 0C, adjusted to over pH 8 with 12 N sodium hydroxide, and extracted with ethyl acetate (500 ml). The organic layer was washed with brine, dried over sodium sulfate, and cocentrated under reduced pressure to yield the title compound (14.8 g).

^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.1 Hz), 1.96-2.22 (4H, m), 2.26-2.41 (3H, m), 2.63-2.85 (5H, m), 3.61-3.96 (2H, m), 6.91 (1H, d, J=7.7 Hz), 7.08 (1H, dt, J=1.1, 7.3 Hz), 7.18-7.37 (7H, m)

Reference Example 42

Reference Example 42-1

N-(3-Cyanophenyl)piperazine

3-Aminobenzonitrile (5.9 g) was dissolved in butanol (60 ml), followed by addition of bis(2-chloroethyl)amine hydrochloride (8.9 g). The mixture was refluxed with stirring for 24 hours and then sodium carbonate (5.3 g) was added. The mixture was refluxed for additional 48 hours. The reaction mixture was cooled to room temperature and the insoluble material was collected by filtration, followed by partition between ethyl acetate and 1 N sodium hydroxide. The organic layer separated was washed with brine 3 times, dried over sodium sulfate, and purified by silica gel column chromatography luting with ethyl acetate/methanol (7/3) to yield the title compound (3.1 g).

(3.85 g). The mixture was refluxed with stirring for 1 hour and then poured into ice-water. The resulting precipitate was collected by filtration, washed with water, and dried to yield 4-(3-chlorophenyl)glutarimide (6.38 g). The glutarimide derivative (6.38 g) obtained was added portionwise to a suspension of lithium aluminum hydride (3.25 g) in THF (90 ml) at 0°C and the mixtute was refluxed for 2 hours. To the reaction mixture cooled at 0°C were added dropwise water (6.5 ml) and 3 N sodium hydroxide (5.2 ml), successively, and the resulting precipitate was removed by filtration. The filtrate was concentrated under reduced pressure to yield the title compound (5.42 g).
^{1}H-NMR ($CDCl_3$) δ: 1.49-1.93 (5H, m), 2.50-2.63 (1H, m), 2.64-2.83 (2H, m), 3.12-3.27 (2H, m), 7.04-7.32 (4H, m)

Reference Example 44

1,2,3,4-Tetrahydro-4-(2-hydroxyethyl)-4-phenylisoquinoline

To a stirred solution of ethyl (3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl) acetate (2.00 g) obtained in Reference Example 26 in THF (20 ml) was added portionwise lithium aluminum hydride (0.49 g) under ice cooling condition.

After completion of the addition, the mixture was heated under reflux for 6 hours. The reaction mixture was cooled to 0°C and water (1.0 ml) and 15% sodium hydroxide (0.8 ml) were added. The resulting precipitate was filtered and the filtrate was dried and concentrated to dryness. The residue obtained was purified by silica gel column chromatography eluting with ethyl acetate/methanol (10/1) to yield the title compound (1.18 g).
Melting point: 116 - 117°C (crystallizing solvent: ethyl acetate/isopropyl ether)

Reference Example 45

2-Acetyl-1,2,3,4-tetrahydro-4-(2-hydroxyethyl)-4-phenylisoquinoline

Compounds in the following Reference Examples 47-1 and 47-2 were obtained in the same manner as in Reference Example 27-1.

Reference Example 47-1: Ethyl (2-methoxymethyl-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate
^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t), 3.23 (1H, d), 3.21 (3H, s), 3.97 (1H, d), 3.95-4.11 (2H, m), 4.28 (2H, q), 4.98 (2H, q), 7.00-7.09 (2H, m), 7.18-7.40 (7H, m)

Reference Example 47-2: Ethyl (3-oxo-4-phenyl-2-propyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate
^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t), 1.08 (3H, t), 1.49-1.70 (2H, m), 3.20 (1H, d), 3.94 (1H, d), 3.30-3.46 (1H, m), 3.54-3.70 (1H, m), 3.90-4.08 (2H, m), 4.22 (2H, s), 7.00-7.09 (2H, m), 7.15-7.40 (7H, m)

Reference Example 48

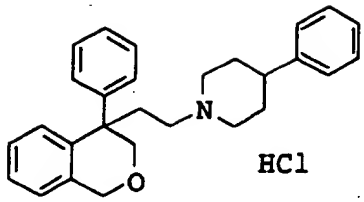
Compounds in the following Reference Examples 48-1 and 48-2 were obtained in the same manner as in Reference Example 28-1.

Reference Example 48-1: (2-Methoxymethyl-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetic acid
^{1}H-NMR ($CDCl_3$) δ: 3.17 (3H, s), 3.24 (1H, d), 3.83 (1H, d), 4.03 (1H, d), 4.31 (1H, d), 4.96 (2H, q), 6.95-7.05 (2H, m), 7.17-7.29 (4H, m), 7.30-7.51 (3H, m)

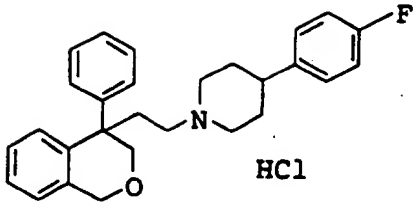
Reference Example 48-2: (3-Oxo-4-phenyl-2-propyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetic acid
^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t), 1.50-1.70 (2H, m), 3.23 (1H, d), 3.70 (1H, d), 3.30-3.47 (1H, m), 3.65-3.80 (1H, m), 4.02 (2H, q), 6.92-7.01 (2H, m), 7.17-7.51 (6H, m), 7.70 (1H, d)

Reference Example 49

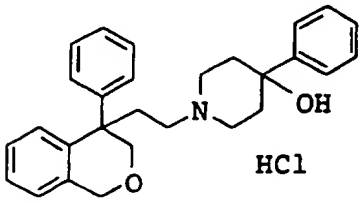
Compounds in the following Reference Examples 49-1 and 49-2 were obtained in the same manner as in Reference Example 29-1.



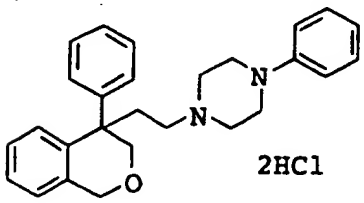
Reference Example 4-1



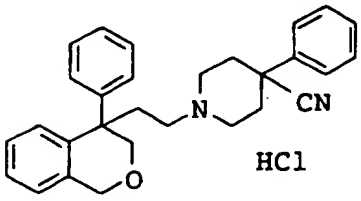
Reference Example 4-6



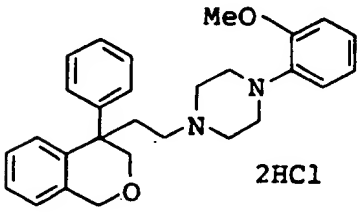
Reference Example 4-2



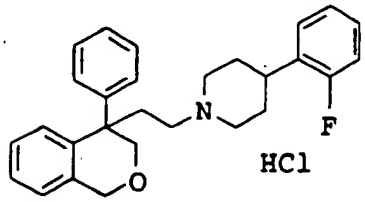
Reference Example 4-7



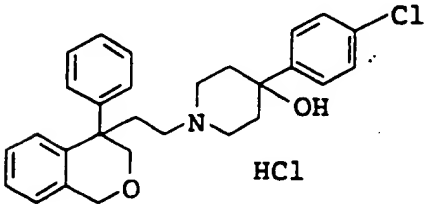
Reference Example 4-3



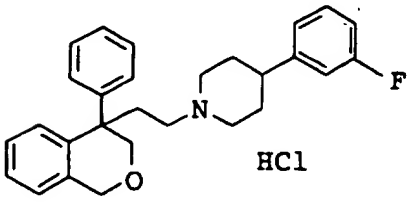
Reference Example 4-8



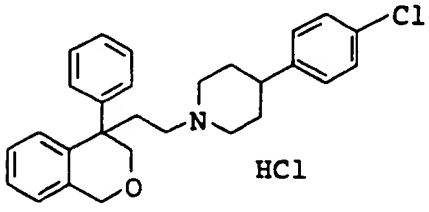
Reference Example 4-4



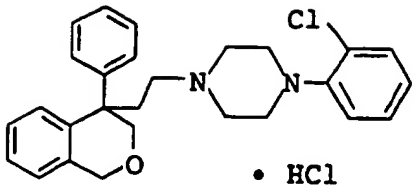
Reference Example 4-9



Reference Example 4-5

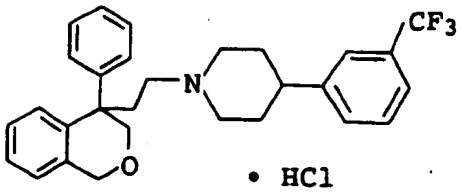


Reference Example 4-10



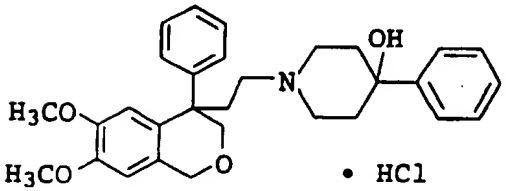
• HCl

Reference Example 13-1



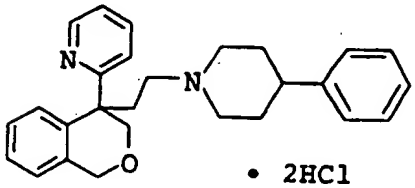
• HCl

Reference Example 13-6



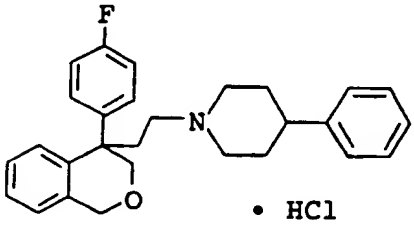
• HCl

Reference Example 13-2



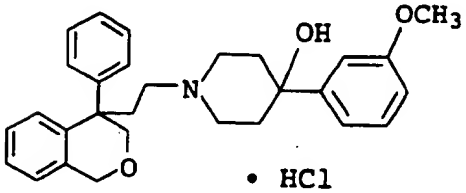
• 2HCl

Reference Example 13-7



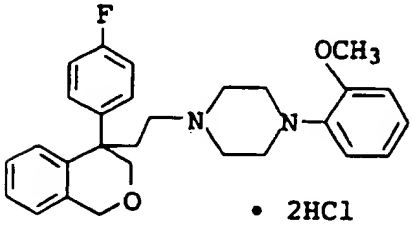
• HCl

Reference Example 13-3



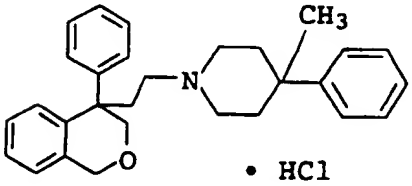
• HCl

Reference Example 13-8



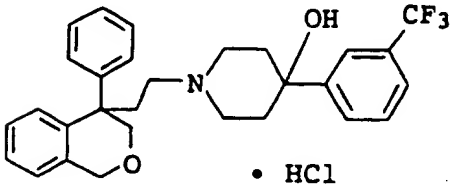
• 2HCl

Reference Example 13-4



• HCl

Reference Example 13-9



• HCl

Reference Example 13-5

(4) Magnesium stearate 3 mg

Total 120 mg

In accordance with a conventional method, the above components (1) through (4) were mixed and filled in a gelatin capsule to yield a capsular preparation.

Example 3

(1) Reference Example Compound 4-1 50 mg

(2) Corn oil 100 mg

Total 150 mg

In accordance with a conventional method, the above components (1) and (2) were mixed and filled in a soft capsule to yield a soft capsular preparation.

Example 4

Example 4-1

1,3-Dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one

A solution of 3-(2-bromoethyl)-1,3-dihydro-3-phenyl-2H-indol-2-one (10.0 g) obtained in Reference Example 21 and 4-phenylpiperidine (10.7 g) in acetonitrile (100 ml) was stirred under heating at 60°C for 14 hours. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was dried with anhydrous sodium sulfate and concentrated. The oily residue obtained was purified by silica gel column chromatography eluting with hexane/ethyl acetate (3/1 to 3/7) and crystallized from ethyl acetate/isopropyl ether to yield the title compound (7.69 g) as a crystal.

Melting point: 156 - 157°C

Example Compounds 4-2 and 4-3 below were obtained in the same manner as in Example 4-1.

Example Compound 4-2: 1,3-Dihydro-3-(2-(4-hydroxy-4-phenylpiperidino)ethyl)-3-phenyl-2H-indol-2-one

Amorphous powder

Example Compound 5-3: 1,3-Dihydro-3-(2-(4-(o-methoxyphenyl)piperazin-1-yl)ethyl)-1-methyl-3-phenyl-2H-indol-2-one dihydrochloride

Amorphous powder

^{1}H-NMR ($CDCl_3$) δ: 2.13-2.38 (5H, m), 2.52-2.68 (2H, m), 2.77-3.05 (5H, m), 3.21 (3H, s), 3.82 (3H, s), 6.80-7.03 (5H, m), 7.08-7.16 (1H, m), 7.23-7.43 (7H, m)

Example 5-4

1,3-Dihydro-1-ethyl-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one hydrochloride

1,3-Dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one (0.4 g) obtained in Example 4-1 was dissolved in THF (5 ml) and potassium tert-butoxide (0.14 g) was added, followed by stirring at room temperature for 15 minutes. To the solution obtained was added ethyl iodide (0.12 ml), followed by stirring at ambient temperature for 2 hours. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with hexane/ethyl acetate (2/1) to yield a light-yellow oily substance, which was then treated with a 4 N solution of hydrogen chloride/ethyl acetate to yield the title compound (0.2 g).

Amorphous powder

^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.1 Hz), 1.49-2.27 (8H, m), 2.32-2.47 (2H, m), 2.66-2.84 (2H, m), 2.87-2.99 (1H, br d), 3.62-3.94 (2H, m), 6.92 (1H, d, J=7.6 Hz), 7.05-7.40 (13H, m)

Example Compounds 5-5 through 5-12 below were obtained in the same manner as in Example 5-4.

Example Compound 5-5: Ethyl (2,3-dihydro-2-oxo-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-1H-indol-1-yl)acetate

^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, d, J=7.0 Hz), 1.51 (3H, d, J=7.0 Hz), 1.67-1.84 (4H, m), 1.88-2.26 (4H, m), 2.33-2.53 (2H, m), 2.63-2.80 (1H, m), 2.86-3.05 (2H, m), 4.59-4.73 (1H, m), 7.04-7.13 (2H, m), 7.16-7.38 (12H, m)

Example Compound 5-11: 1,3-Dihydro-3-phenyl-1-phenylmethyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one hydrochloride

Amorphous powder

^{1}H-NMR ($CDCl_3$) δ: 1.58-1.84 (4H, m), 1.88-1.99 (2H, m), 2.00-2.32 (2H, m), 2.35-2.54 (2H, m), 2.72-2.89 (2H, m), 2.90-3.03 (1H, m), 4.82 (1H, d, J=15.4 Hz), 5.06 (1H, d, J=15.4 Hz), 6.79 (1H, d, J=7.7 Hz), 7.03-7.13 (1H, m), 7.17-7.43 (17H, m)

Example Compound 5-12: 1-Cyclopropylmethyl-1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one hydrochloride

Amorphous powder

^{1}H-NMR ($CDCl_3$) δ: 0.36-0.58 (4H, m), 1.56-1.82 (4H, m), 1.84-2.03 (2H, m), 2.07-2.32 (2H, m), 2.34-2.52 (2H, m), 2.67-3.00 (4H, m), 3.59 (1H, dd, J=7.0, 14.3 Hz), 3.70 (1H, dd, J=7.0, 14.3 Hz), 6.96-7.40 (14H, m)

Example 5-13

1,3-Dihydro-1-ethyl-3-(2-(4-hydroxy-4-phenylpiperidino)ethyl)-3-phenyl-2H-indol-2-one hydrochloride

1,3-Dihydro-3-(2-(4-hydroxy-4-phenylpiperidino)ethyl)-3-phenyl-2H-indol-2-one (0.43 g) obtained in Example 4-2 was dissolved in THF (5 ml) and potassium tert-butoxide (0.10 g) was added, followed by stirring at room temperature for 15 minutes. To the solution obtained was added ethyl iodide (0.34 g), followed by stirring at ambient temperature for 2 hours. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and concentrated under reduced pressure to yield an amorphous powder, which was then

Example 5-16

1,3-Dihydro-3-(2-(4-(o-methoxyphenyl)piperazin-1-yl)ethyl)-3-phenyl-1-propyl-2H-indol-2-one dihydrochloride

The title compound was obtained in the same manner as in Example 5-15.

Melting point: 149 - 152°C (recrystallizing solvent: ethanol)

Example 5-17

1,3-Dihydro-1-(2-(dimethylamino)ethyl)-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one dihydrochloride

To a suspension of 1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one (0.30 g) obtained in Example 4-1 and N,N-dimethyl-2-chloroethylamine hydrochloride (0.16 g) in 4-methyl-2-pentanone (3.2 ml) was added an 18% aqueous solution of sodium hydroxide (0.7 ml), followed by heating under reflux for 4 hours. A saturated aqueous solution of sodium hydrogen carbonate was added, followed by extraction with ethyl acetate. The extract was dried with anhydrous sodium sulfate and concentrated. The residue obtained was purified by silica gel column chromatography eluting with ethyl acetate/methanol (10/1). The oily material obtained was treated with a 4 N solution of hydrogen chloride/ethyl acetate to yield the title compound (0.27 g) as an amorphous powder.

^{1}H-NMR ($CDCl_3$) δ: 1.48-1.83 (4H, m), 1.84-2.27 (4H, m), 2.30 (6H, s), 2.32-2.66 (4H, m), 2.67-2.85 (2H, m), 2.88-3.02 (1H, m), 3.71-4.02 (2H, m), 6.94 (1H, d, J=7.7 Hz), 7.04-7.41 (13H, m)

Example Compounds 5-18 through 5-20 below were obtained in the same manner as in Example 5-17.

Example Compound 5-18: 1,3-Dihydro-1-(3-(dimethylamino)propyl)-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one dihydrochloride

Example 5-22

1,3-Dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-1-(3-phthalimidopropyl)-2H-indol-2-one hydrochloride

The title compound was obtained in the same manner as in Example 5-21.

Amorphous powder

^{1}H-NMR ($CDCl_3$) δ: 1.53-1.80 (4H, m), 1.84-1.99 (2H, m), 2.00-2.29 (4H, m), 2.31-2.49 (2H, m), 2.68-2.86 (2H, m), 2.88-2.99 (1H, m), 3.68-3.99 (4H, m), 6.90 (1H, d, J=7.7 Hz), 7.05-7.41 (13H, m), 7.68-7.76 (2H, m), 7.79-7.88 (2H, m)

Example 5-23

1-Acetyl-1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one

1,3-Dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one (0.4 g) obtained in Example 4-1 was dissolved in acetic anhydride (10 ml) and 4-(N,N-dimethylamino)pyridine (6 mg) was added, followed by stirring at 50°C for 2 hours. After being diluted with ethyl acetate, the solution obtained was washed with 1 N sodium hydroxide, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with hexane/ethyl acetate (3/2) to yield a colorless oily residue, which was then crystallized from isopropyl ether to yield the title compound (0.2 g).

Melting point: 109 - 111°C

Example 5-24

1-(2-Aminoethyl)-1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one dihydrochloride

To a solution of 1,3-dihydro-3-phenyl-3-(2-(4-phenylpip ridino)ethyl)-1-(2-phthalimidoethyl)-2H-indol-2-one (0.47 g) obtained in Example 5-21 in methanol (2 ml)

hydrogen chloride/ethyl acetate to yield the title compound (4.37 g) as an amorphous powder.

^{1}H-NMR ($CDCl_3$) δ: 1.69-1.84 (4H, m), 1.88-2.03 (2H, m), 2.04-2.32 (2H, m), 2.34-2.51 (2H, m), 2.59-2.76 (1H, m), 2.86-3.06 (8H, m), 7.03-7.39 (14H, m)

Example Compounds 6-2 and 6-3 below were obtained in the same manner as in Example 6-1.

Example Compound 6-2: 1,3-Dihydro-1-(dimethylamino)-3-(2-(4-hydroxy-4-phenylpiperidino)ethyl)-3-phenyl-2H-indol-2-one hydrochloride

Amorphous powder

^{1}H-NMR ($CDCl_3$) δ: 1.53-1.68 (2H, m), 1.71 (1H, br s), 1.95-2.23 (3H, m), 2.24-2.52 (4H, m), 2.60-2.78 (3H, m), 2.98 (6H, m), 7.03-7.23 (2H, m), 7.24-7.40 (10H, m), 7.43-7.52 (2H, m)

Example Compound 6-3: 1,3-Dihydro-1-(dimethylamino)-3-(2-(4-(o-methoxyphenyl)piperazin-1-yl)ethyl)-3-phenyl-2H-indol-2-one dihydrochloride

Melting point: 114 - 116°C (recrystallizing solvent: ethyl acetate)

Example 7

Example 7-1

2-Methyl-3-oxo-4-phenyl-4-(2-(4-phenylpiperidino)ethyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

A mixture of 4-(2-iodoethyl)-2-methyl-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinoline (70 mg) (Reference Example 30-1), 4-phenylpiperidine (44 mg) and potassium carbonate (38 mg) was stirred in acetonitrile (5 ml) under heating at 60°C overnight. The insoluble material in the reaction mixture was filtered off and the filtrate was concentrated to dryness. The residue obtained was purified by silica gel column chromatography and treated with a 4N solution of hydrogen chloride/ethyl acetate to afford the title compound (50 mg) after crystallizing the salt from isopropyl ther.

methanol (10 ml) and 1N sodium hydroxide (3 ml) was added, follow d by stirring at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate and the organic layer was washed with brine. The organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography eluting with hexane/ethyl acetate (1/9) to yield the title compound (390 mg) as an amorphous powder.

^{1}H-NMR ($CDCl_3$) δ: 1.65-2.48 (11H, m), 2.68 (1H, br d, 11.4 Hz), 2.76-2.81 (1H, m), 3.02 (1H, br d, J=10.4 Hz), 3.92 (4H, s), 6.98 (1H, d, J=8.0 Hz), 7.18 -7.40 (13H, m)

Example 8-2

3-(2-(4-Acetyl-4-phenylpiperidino)ethyl)-1,3-dihydro-1-methyl-3-phenyl-2H-indol-2-one

The title compound was obtained in the same manner as in Example 5-1.

^{1}H-NMR ($CDCl_3$) δ: 1.65-2.38 (10H, m), 1.84 (3H, s), 2.57-2.83 (2H, m), 3.14 (3H, s), 6.88 (1H, t, J=7.5 Hz), 7.06-7.38 (13H, m)

Example 8-3

1-Ethyl-1,3-dihydro-3-phenyl-3-(2-(4-(3-trifluoromethylphenyl)piperidino)ethyl)-2H-indol-2-one hydrochloride

3-(2-(Bromoethyl)-1-ethyl-1,3,-dihydro-3-phenyl-2H-indol-2-one (1.0 g) obtained in Reference Example 37-1 was dissolved in DMF (10 ml) and 4-(3-trifluoromethylphenyl)piperidine (0.7 g), potassium carbonate (0.6 g), and potassium iodide (0.05 g) were added, followed by stirring at 60°C for 48 hours. The reaction mixture was diluted with ethyl acetate (50 ml) and the organic layer was washed three times with brine (50 ml). The organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off under reduced

hydrochloride (1.4 g), potassium carbonate (0.8 g), and potassium iodide (0.05 g) were added, followed by stirring at 60°C for 48 hours. The reaction mixture was diluted with ethyl acetate (50 ml) and the organic layer was washed three times with brine (50 ml). The organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography eluting with hexane/ethyl acetate (2/1) to yield an oil. The oily material obtained was treated with a 4 N solution of hydrogen chloride/ethyl acetate, and the formed salt was crystallized from ethyl acetate/diethyl ether to yield the title compound (0.37 g).

Melting point: 122 - 124°C

Compounds in Examples 8-6 through 8-23 below were obtained in the same manner as in Example 8-5.

Example 8-6: 1-Ethyl-1,3-dihydro-3-phenyl-3-(2-(4-(4-pyridyl)piperazin-1-yl)ethyl)-2H-indol-2-one dihydrochloride

Amorphours powder

^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.1 Hz), 2.12-2.90 (5H, m), 3.02-4.02 (9H, m), 6.63 (2H, t, J=6.2 Hz), 6.95 (1H, dd, J=3.3, 7.7 Hz), 7.10 (1H, t, J=7.5 Hz), 7.22-7.39 (5H, m), 8.27 (2H, br)

Example 8-7: 1-Ethyl-1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperazin-1-yl)ethyl)-2H-indol-2-one dihydrochloride

Amorphours powder

^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.1 Hz), 2.25-2.63 (6H, m), 2.68-2.90 (2H, m), 2.94-3.21 (4H, m), 3.56-3.93 (2H, m), 6.79-6.98 (4H, m), 7.04-7.45 (10H, m)

Example 8-8: 1-Ethyl-1,3-dihydro-3-(2-(4-(4-methoxyphenyl)piperazin-1-yl)ethyl)-3-phenyl-2H-indol-2-one dihydrochloride

Amorphours powder

^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, dt, J=2.1, 7.1 Hz), 2.07-2.41 (4H, m), 2.45-2.59 (2H, m), 2.63-3.04 (6H, m), 3.58-3.98

Example 8-15: 3-(2-(4-(4-Acetylphenyl)piperazin-1-yl)ethyl)-1-ethyl-1,3-dihydro-3-phenyl-2H-indol-2-one dihydrochloride
Melting point: 134 - 136°C (crystallizing solvent: ethyl acetate)

Example 8-16: 1-Ethyl-1,3-dihydro-3-(2-(4-(3-nitrophenyl)piperazin-1-yl)ethyl)-3-phenyl-2H-indol-2-one dihydrochloride
Melting point: 149 - 152°C (crystallizing solvent: ethyl acetate)

Example 8-17: 3-(2-(4-(3-Cyanophenyl)piperazin-1-yl)ethyl)-1-ethyl-1,3-dihydro-3-phenyl-2H-indol-2-one dihydrochloride
Melting point: 128 - 131°C (crystallizing solvent: ethyl acetate)

Example 8-18: 1-Ethyl-3-(2-(4-(2-fluorophenyl)piperazin-1-yl)ethyl)-1,3-dihydro-3-phenyl-2H-indol-2-one dihydrochloride
Melting point: 116 - 118°C (crystallizing solvent: ethyl acetate)

Example 8-19: 1-Ethyl-3-(2-(4-(3-fluorophenyl)piperazin-1-yl)ethyl)-1,3-dihydro-3-phenyl-2H-indol-2-one dihydrochloride
Melting point: 158 - 161°C (crystallizing solvent: ethyl acetate)

Example 8-20: 1-Ethyl-3-(2-(4-(4-fluorophenyl)piperazin-1-yl)ethyl)-1,3-dihydro-3-phenyl-2H-indol-2-one dihydrochloride
Melting point: 169 - 172°C (crystallizing solvent: ethyl acetate)

Example 8-21: 1-Ethyl-1,3-dihydro-3-(2-(4-(3-methoxyphenyl)piperazin-1-yl)ethyl)-3-phenyl-2H-indol-2-one dihydrochloride
Melting point: 138 - 140°C (crystallizing solvent: ethyl acetate)

3.61 (2H, m), 3.67-3.93 (3H, m), 3.99-4.11 (1H, m), 7.02-7.41 (14H, m)

Example 8-26

1-(5-Acetyloxypentyl)-1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one hydrochloride

The title compound was obtained in the same manner as in Example 5-4.

Amorphous powder

^{1}H-NMR ($CDCl_3$) δ: 1.32-1.48 (2H, m), 1.50-1.82 (8H, m), 1.83-2.00 (2H, m), 2.01 (3H, s), 2.04-2.28 (2H, m), 2.31-2.48 (2H, m), 2.66-2.84 (2H, m), 2.88-3.01 (1H, m), 3.56-3.72 (1H, m), 3.76-3.93 (1H, m), 4.00 (2H, t, J=6.7 Hz), 6.91 (1H, d, J=7.7 Hz), 7.05-7.39 (13H, m)

Example 8-27

1,3-Dihydro-1-(3-morpholinopropyl)-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one dihydrochloride

A solution of 1-(3-bromopropyl)-1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one (0.5 g) obtained in Example 8-24 and morpholine (0.25 g) in acetonitrile (5 ml) was stirred at 80°C for 24 hours. To the reaction mixture was added a saturated sodium bicarbonate (5 ml) and extracted with ethyl acetate. The extract was dried with anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography eluting with ethyl acetate/methanol (10/1). The oily material obtained was treated with a 4 N solution of hydrogen chloride/ethyl acetate, and the formed salt was crystallized by ethyl acetate to yield the title compound (0.38 g).

Melting point: 205 - 209°C

Examples 8-28 and 8-29

Example 8-30

1-(3-(4-Ethoxycarbonylpiperazin-1-yl)propyl)-1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one dihydrochloride

1-(3-bromopropyl)-1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperidino)-2H-indol-2-one (0.78 g) obtained in Example 8-24 and ethyl 1-piperazinecarboxylate (0.72 g) were reacted in the same manner as in Example 8-27 to yield the title compound (0.43 g).

Melting point: 127 - 129°C (crystallizing solvent: ethyl acetate)

Example 8-31

1,3-Dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-1-(3-(piperazin-1-yl)propyl)-2H-indol-2-one trihydrochloride

A mixture of 1-(3-(4-ethoxycarbonylpiperazin-1-yl)propyl)-1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one (0.30 g) (free form of the compound obtained in Example 8-30) and conc. hydrochloric acid (3.0 ml) in ethanol (3.0 ml) was stirred at 80°C for 24 hours. Then, hydrochloric acid (3.0 ml) was added to the resulting mixture and stirring was continued at 80°C for 38 hours. The reaction mixture was made basic by a solution of sodium hydroxide and extracted with ethyl acetate. The extract was dried with anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The oily material obtained was treated with a 4 N solution of hydrogen chloride/ethyl acetate, and the formed salt was crystallized from ethanol/ethyl acetate to yield the title compound (0.14 g).

Melting point: 181 - 184°C

Compounds in Examples 8-32 through 8-34 below were obtained in the same manner as in Example 5-1.

Example 8-32: 1-Ethyl-5-fluoro-1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one hydrochloride

g) (free form of the compound obtained in Example 8-35) in acetonitrile (5.0 ml) were added acetic anhydride (0.13 g) and triethylamine (0.17 ml) sequentially. The resulting mixture was stirred at room temperature for 1 hour. A saturated aqueous solution of sodium hydrogen carbonate was added, followed by extraction with ethyl acetate. The extracts were dried with anhydrous sodium sulfate and concentrated. The residue obtained was purified by silica gel column chromatography eluting with hexane/ethyl acetate (1/3) to yield an oily substance. The oily material obtained was treated with a 4 N solution of hydrogen chloride/ethyl acetate and crystallized from ethyl acetate to yield the title compound (0.58 g).
Melting point: 163 - 165°C

Example 8-37
1,3-Dihydro-1-(5-hydroxypentyl)-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one hydrochloride

The title compound was obtained in the same manner as in Example 8-1.
Amorphous powder
^{1}H-NMR ($CDCl_3$) δ: 1.33-1.48 (2H, m), 1.51-1.84 (9H, m), 1.85-2.03 (2H, m), 2.04-2.29 (2H, m), 2.31-2.48 (2H, m), 2.68-2.87 (2H, m), 2.89-3.02 (1H, m), 3.57 (2H, t, J=6.2 Hz), 3.61-3.74 (1H, m), 3.75-3.92 (1H, m), 6.92 (1H, d, J=8.1 Hz), 7.05-7.40 (13H, m)

Example 9
Example 9-1
1-(Dimethylamino)-1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperazin-1-yl)ethyl)-2H-indol-2-one dihydrochloride

The title compound was obtained in the same manner as in Example 6-1.
Melting point: 177 - 179°C (crystallizing solvent: ethyl acetate)

Example 9-5: 1,3-Dihydro-3-phenyl-1-piperidino-3-(2-(4-(3-trifluoromethylphenyl)piperazin-1-yl)ethyl)-2H-indol-2-one dihydrochloride

Amorphous powder

^{1}H-NMR ($CDCl_3$) δ: 1.16-1.42 (1H, m), 1.48-1.82 (5H, m), 2.04-2.56 (7H, m), 2.62-2.79 (1H, m), 2.89-3.23 (6H, m), 3.49-3.78 (2H, m), 6.97-7.38 (13H, m)

Example 9-6

1-(Diethylamino)-1,3-dihydro-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one hydrochloride

To a solution of 3-(2-bromoethyl)-1-(diethylamino)-1,3-dihydro-3-phenyl-2H-indol-2-one (0.50 g) obtained in Reference Example 39-2 in DMF (5.0 ml) were added 4-phenylpiperidine (0.25 g), potassium carbonate (0.21 g), and potassium iodide (0.05 g). The mixture was stirred at 80°C for 48 hours. A saturated aqueous sodium hydrogen carbonate was added, followed by extraction with ethyl acetate. The residue obtained was purified by silica gel column chromatography eluting with hexane/ethyl acetate (4/1) to yield an oily substance. The oily material obtained was treated with a 4 N solution of hydrogen chloride/ethyl acetate to yield the title compound (0.46 g).

Amorphous powder

^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.3 Hz), 1.10 (3H, t, J=7.4 Hz), 1.66-1.86 (4H, m), 1.90-2.09 (2H, m), 2.10-2.20 (1H, m), 2.22-2.33 (1H, m), 2.34-2.54 (2H, m), 2.59-2.77 (1H, m), 2.87-3.15 (4H, m), 3.38-3.68 (2H, m), 6.99-7.38 (14H, m)

Compounds in Examples 9-7 through 9-9 below were obtained in the same manner as in Example 9-6.

Example 9-7: 1-(Diethylamino)-1,3-dihydro-3-(2-(4-hydroxy-4-phenylpiperidino)ethyl)-3-phenyl-2H-indol-2-one hydrochloride

Amorphous powder

Compounds in Examples 10-1 through 10-7 below were obtained in the same manner as in Example 7-1.

Example 10-1: 2-Methoxymethyl-3-oxo-4-phenyl-4-(2-(4-phenylpiperidino)ethyl)-1,2,3,4-tetrahydroisoquinoline
Melting point: 113 - 114°C (crystallizing solvent: ethyl acetate/isopropyl ether)

Example 10-2: 4-(2-(4-Hydroxy-4-phenylpiperidino)ethyl)-2-methoxymethyl-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinoline
Melting point: 164 - 165°C (crystallizing solvent: ethyl acetate/isopropyl ether)

Example 10-3: 2-Methoxymethyl-4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride
Melting point: 172 - 176°C (crystallizing solvent: ethyl acetate/isopropyl ether)

Example 10-4: 4-(2-(4-(2-Methoxyphenyl)piperazin-1-yl)ethyl)-3-oxo-4-phenyl-2-propyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride
Melting point: 154 - 158°C (crystallizing solvent: ethyl acetate/isopropyl ether)

Example 10-5: 3-Oxo-4-phenyl-4-(2-(4-phenylpiperidino)ethyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline
Melting point: 112 - 114°C (crystallizing solvent: ethyl acetate/isopropyl ether)

Example 10-6: 4-(2-(4-Hydroxy-4-phenylpiperidino)ethyl)-3-oxo-4-phenyl-2-propyl-1,2,3,4-tetrahydroisoquinoline
Melting point: 174 - 175°C (crystallizing solvent: ethyl acetate/methanol)

Example 10-7: 2-Ethyl-4-(2-(4-(3-fluorophenyl)piperidino)ethyl)-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride
Amorphous powder

Example 11-3: 3-(2-(4-(2-Acetylph nyl)piperazin-1-yl)ethyl)-1-ethyl-1,3-dihydro-3-phenyl-2H-indol-2-one dihydrochloride
Melting point: 108 - 110°C (crystallizing solvent: ethyl acetate/diethyl ether)

Example 11-4: Methyl 2-(4-(2-(1-ethyl-2,3-dihydro-2-oxo-3-phenyl-1H-indol-3-yl)ethyl)piperazin-1-yl)benzoate dihydrochloride
Melting point: 146 - 151°C (crystallizing solvent: ethyl acetate/isopropyl ether)

Example 11-5: Ethyl 4-(4-(2-(1-ethyl-2,3-dihydro-2-oxo-3-phenyl-1H-indol-3-yl)ethyl)piperazin-1-yl)benzoate dihydrochloride
Melting point: 119 - 124°C (crystallizing solvent: ethyl acetate/isopropyl ether)

Example 11-6: 1-Ethyl-1,3-dihydro-3-(2-(4-(2-nitrophenyl)piperazin-1-yl)ethyl)-3-phenyl-2H-indol-2-one hydrochloride
Melting point: 160 - 161°C (crystallizing solvent: ethyl acetate/methanol)

Example 11-7: 1-Ethyl-1,3-dihydro-3-(2-(4-(4-nitrophenyl)piperazin-1-yl)ethyl)-3-phenyl-2H-indol-2-one dihydrochloride
Melting point: 142 - 144°C (crystallizing solvent: ethyl acetate/methanol)

Example 11-8: 1-Ethyl-1,3-dihydro-3-phenyl-3-(2-(4-(4-trifluoromethylphenyl)piperazin-1-yl)ethyl-2H-indol-2-one dihydrochloride
Melting point: 131 - 134°C (crystallizing solvent: ethyl acetate)

Example 12
Example 12-1
1-(2-(1-(Dimethylamino)-2,3-dihydro-2-oxo-3-phenyl-1H-indol-3-yl)ethyl)-4-ph nylpiperidine 1-oxide

additional 48 hours, a saturated aqueous sodium hydrogen carbonate was added, followed by extraction with ethyl acetate. The extracts were washed with brine, dried with anhydrous sodium sulfate, and concentrated. The residue was disolved in THF (10 ml) and 1 N aqueous sodium hydroxide (4.0 ml) and acetic anhydride (0.35 g) was added dropwise to the solution under ice cooling condition. The mixture was stirred at room temperature for 38 hours. Water was added, followed by extraction with ethyl acetate. The extracts were dried with anhydrous sodium sulfate and concentrated. The residue obtained was purified by silica gel column chromatography eluting with ethyl acetate/methanol (10/1) to yield an oily substance. The oily material obtained was treated with a 4 N solution of hydrogen chloride/ethyl acetate to yield the title compound (0.42 g).

Amorphous powder

^{1}H-NMR ($CDCl_3$) δ: 1.73 and 2.15 (3H, s and s), 1.81-1.94 (4H, m), 2.36-2.94 (8H, m), 3.10-3.33 (2H, m), 3.68-3.88 (1H, m), 4.20-5.01 (2H, m), 7.04-7.38 (14H, m)

Example 14

3-Oxo-4-phenyl-4-(2-(4-phenylpiperidino)ethyl)-1,2,3,4-tetrahydroisoquinoline

To a solution of 2-methoxymethyl-3-oxo-4-phenyl-4-(2-(4-phenylpiperidino)ethyl)-1,2,3,4-tetrahydroisoquinoline (0.12 g) obtained in Example 10-1 in methanol (5.0 ml) was added hydrochloric acid (0.5 ml). The resulting mixture was refluxed for 3 days. Methanol was removed in vacuo and the residue was diluted with water. The solution was basified with aqueous ammonia and the precipitate was collected by filtration. The crude crystalline was recrystallized from DMF/water to yield the title compound (90 mg).

Melting point: 250 - 252°C

acetate (1/1) to yield an oily substance. Th oily material obtained was treated with a 4 N solution of hydrogen chloride/ethyl acetate, and the formed salt was crystallized from ethyl acetate/diethyl ether to yield th title compound (0.17 g).

Melting point: 174 - 177°C

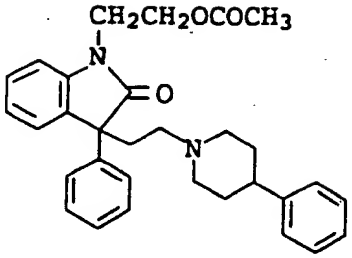
Example 15-4

1-Ethyl-1,3-dihydro-3-(2-(4-(3-(dimethylamino)phenyl)piperazin-1-yl)ethyl)-3-phenyl-2H-indol-2-one trihydrochloride

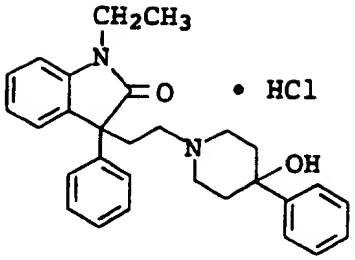
To a solution of 3-(2-(4-(3-aminophenyl)piperazin-1-yl)ethyl)-1-ethyl-1,3-dihydro-3-phenyl-2H-indol-2-one (free form of the compound obtained in Example 8-35) (0.64 g) in acetonitrile (5.0 ml) were added formalin (0.90 ml) and sodium cyanoborohydride (0.21 g) sequentially. Acetic acid (0.11 ml) was added dropwise to the mixture and the resulting mixture was stirred at room temperature for 4 hours. Sodium cyanoborohydride (0.21 g) was added and the mixture was stirred at room temperature for additional 14 hours. A saturated aqueous sodium hydrogen carbonate was added to the resulting mixture, followed by extraction with ethyl acetate. The extracts were dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography eluting with hexane/ethyl acetate (1/1) to yield an oily substance. The oily material obtained was treated with a 4 N solution of hydrogen chloride/ethyl acetate, and the formed salt was crystallized from ethyl acetate/diethyl ether to yield the title compound (0.43 g).

Melting point: 123 - 126°C

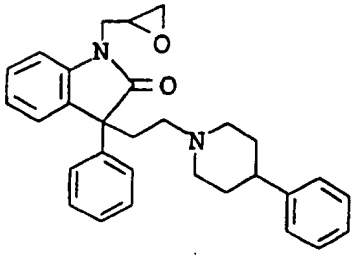
The chemical structural formulas of the compounds obtained in Examples 4 through 15 are shown below.



Example 5-8



Example 5-13



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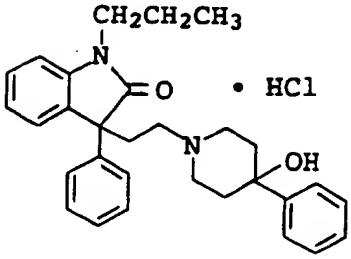
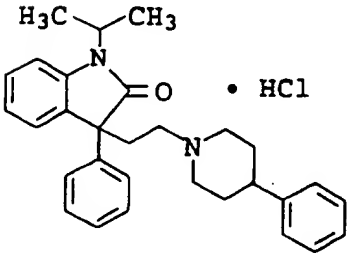
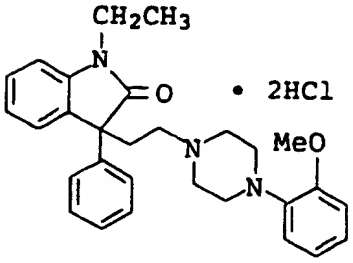


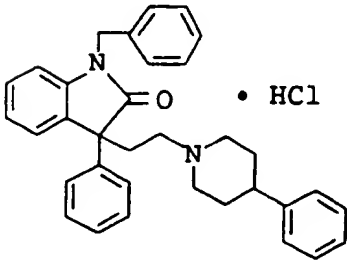
Example 5-14



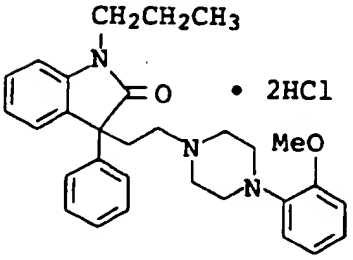
Example 5-10



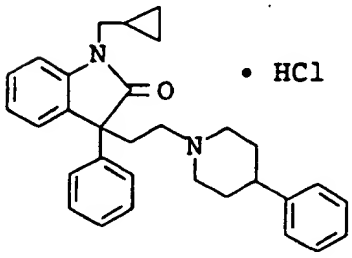
Example 5-15



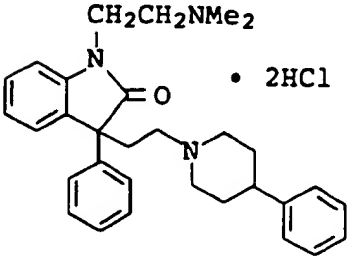
Example 5-11



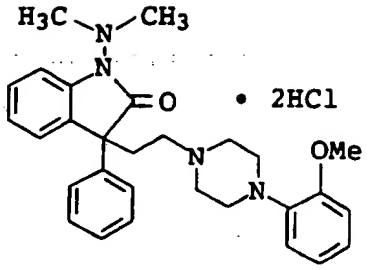
Example 5-16



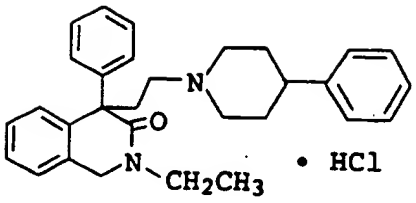
Example 5-12



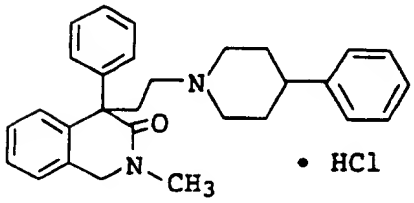
Example 5-17



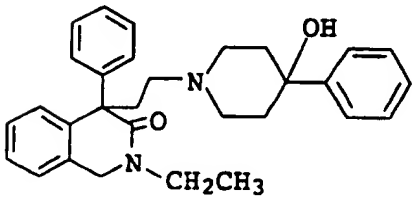
Example 6-3



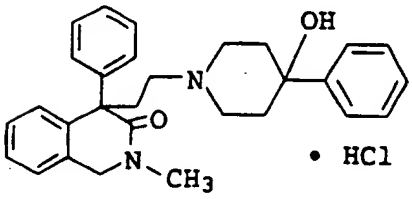
Example 7-4



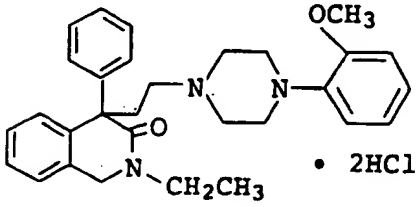
Example 7-1



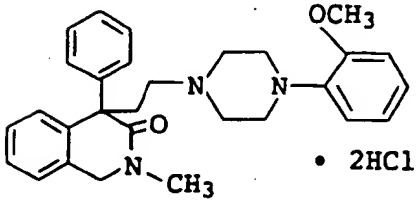
Example 7-5



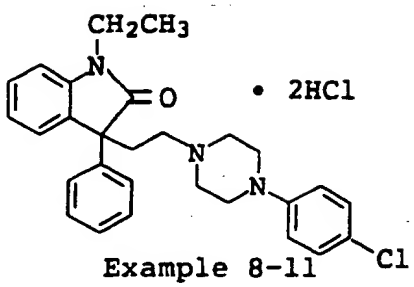
Example 7-2



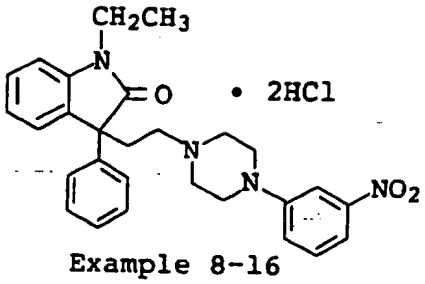
Example 7-6



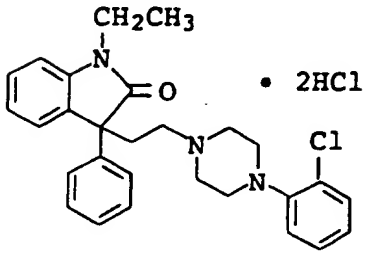
Example 7-3



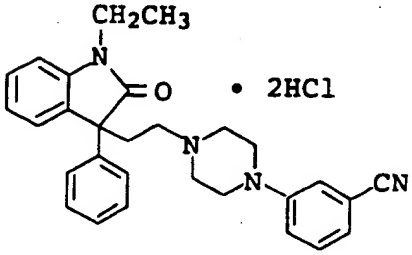
Example 8-11



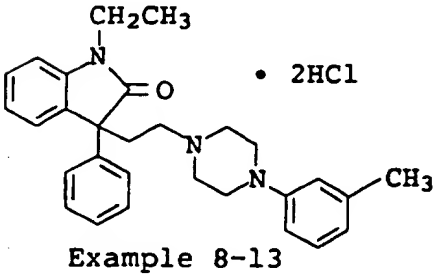
Example 8-16



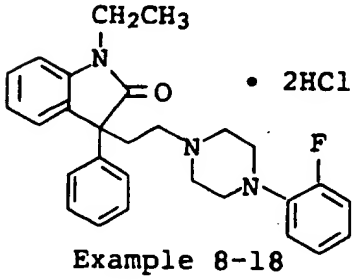
Example 8-12



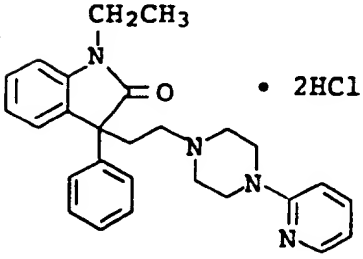
Example 8-17



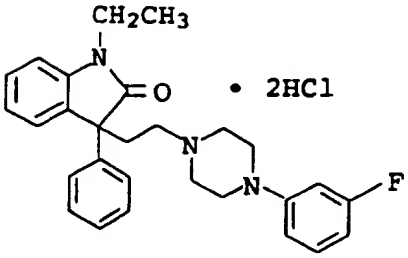
Example 8-13



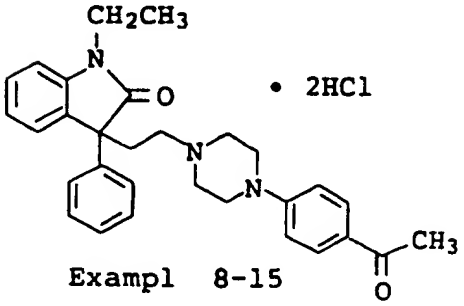
Example 8-18



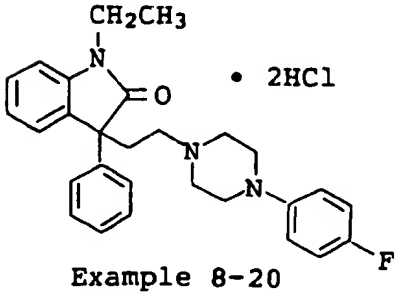
Example 8-14



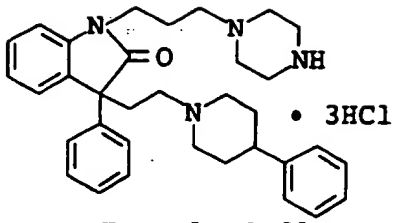
Example 8-19



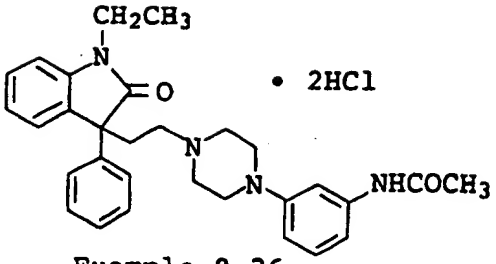
Exampl 8-15



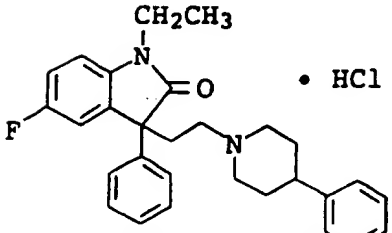
Example 8-20



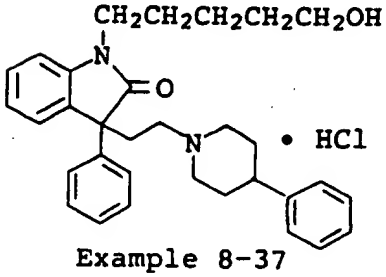
Example 8-31



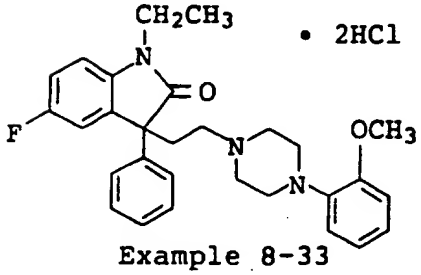
Example 8-36



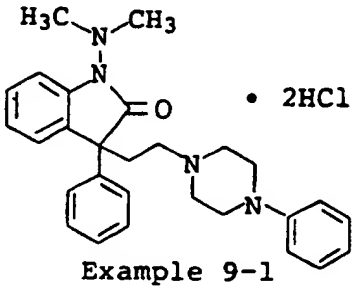
Example 8-32



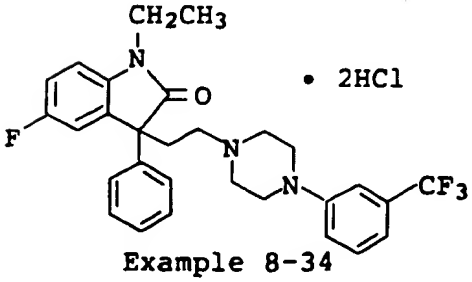
Example 8-37



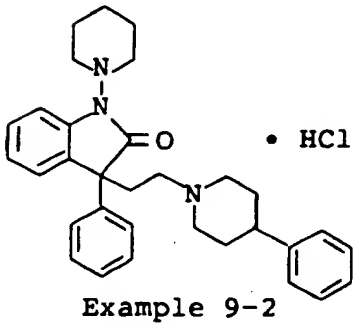
Example 8-33



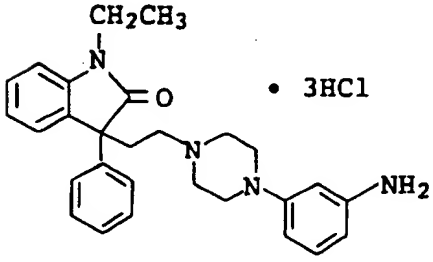
Example 9-1



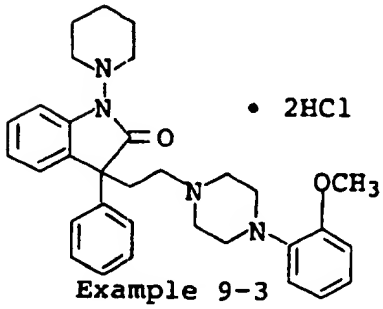
Example 8-34



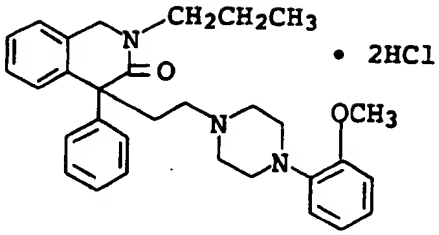
Example 9-2



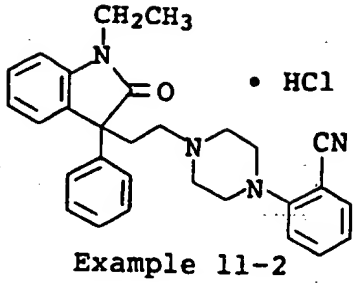
Example 8-35



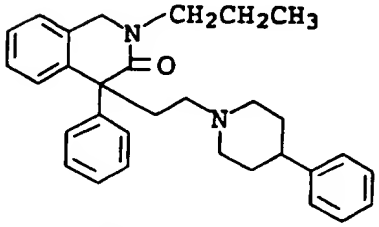
Example 9-3



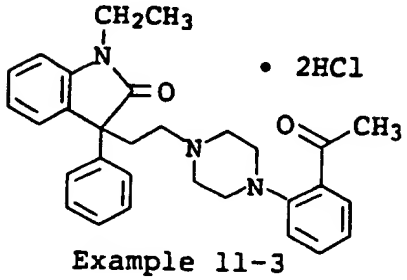
Example 10-4



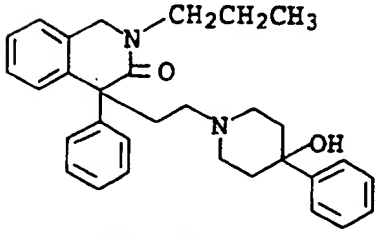
Example 11-2



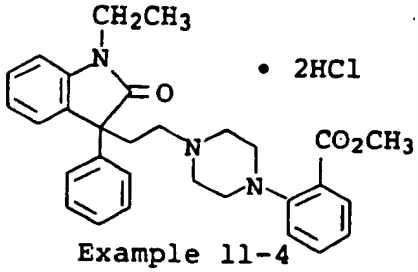
Example 10-5



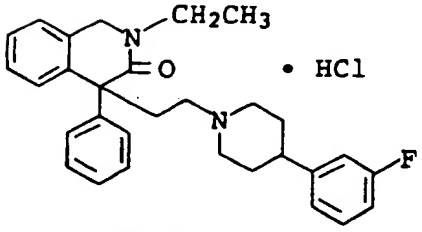
Example 11-3



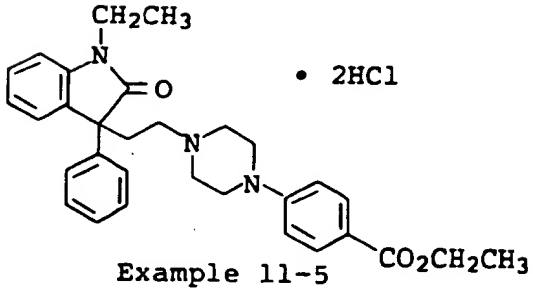
Example 10-6



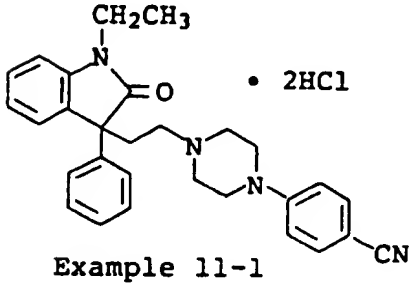
Example 11-4



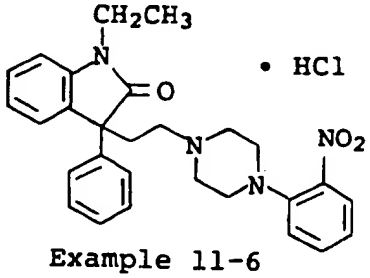
Example 10-7



Example 11-5



Example 11-1



Example 11-6

Example 16

(1)	Example Compound 7-1	50 mg
(2)	Lactose	34 mg
(3)	Corn starch	10.6 mg
(4)	Corn starch (pasty)	5 mg
(5)	Magnesium stearate	0.4 mg
(6)	Carboxymethyl cellulose calcium	20 mg
	Total	120 mg

In accordance with a conventional method, the above components (1) through (6) were mixed and tableted using a tableting machine to yield a tablet.

Example 17

(1)	Example Compound 5-4	50 mg
(2)	Finely powdered cellulose	30 mg
(3)	Lactose	37 mg
(4)	Magnesium stearate	3 mg
	Total	120 mg

In accordance with a conventional method, the above components (1) through (4) were mixed and filled in a gelatin capsule to yield a capsular preparation.

Text Example 1

Action on distension-induced rhythmic bladder contractions in urethane-anesthetized guinea pigs

Five to ten male guinea pigs (weighing 250 to 300 g) per group were anesthetized with urethane (1.2 g/kg, i.p.); a median incision was made in the lower abdomen and the urethra was ligated. A polyethylene cannula (PE-90) was inserted into the urinary bladder to allow injection of physiological saline and measurement of the bladder's inner pressure. The cannula was fixed in place with a quick adhesive (Aron Alpha (trade name)). The bladder's inner pressure was recorded on a polygraph via a pressure transducer. A given amount (about 3 ml) of physiological saline, warmed to 38°C, was injected into the bladder;

INDUSTRIAL APPLICABILITY

Compounds (I) and (Ia) are useful as a pharmaceutical composition for controlling micturition because they possess excellent micturition reflex-suppressing activity and are low in toxicity. They are also effective as prophylactic and therapeutic agents for lower urinary tract dysfunctions such as pollakiuria and urinary incontinence.

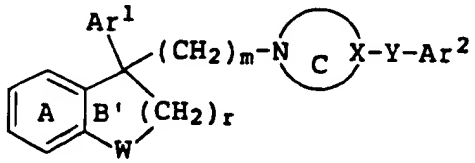
alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino;
ring B is a 4- to 7-membered carbocyclic or heterocyclic ring optionally containing 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino, di-C_{7-16} aralkylamino and oxo;
ring C is a 4- to 7-membered nitrogen-containing heterocyclic ring containing at least one nitrogen atom which may be oxidized, in addition to carbon atoms, and optionally containing 1 to 3 hetero atoms selected from oxygen, nitrogen and sulfur atoms, which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino,

5. A composition of Claim 1, wherein m is 2.

6. A composition of Claim 1, which is for the prophylaxis or treatment of the lower urinary tract dysfunctions.

7. A composition of Claim 6, wherein the lower urinary tract dysfunctions is urinary incontinence or pollakiuria.

8. A compound of the formula:



wherein ring A represents an optionally substituted benzene ring;
ring B' represents an optionally substituted 5- to 7-membered carbocyclic or heterocyclic ring;
W represents a divalent group of the formula: $-CH_2-CH_2-$, $-CH=CH-$, $-CO-O-$, $-CO-NR^6-$, $-NR^6-CO-$, $-N=CH-$, $-CH_2-S(O)_p-$, $-N=N-$, $-NR^6-SO_2-$, $-SO_2-NR^6-$, $-NR^6-NR^{6a}-$, $-CH_2-NR^6-CO-$ or $-CO-NR^6-CO-$
wherein R^6 and R^{6a} each represents a hydrogen atom, an optionally substituted hydrocarbon group, acyl or an optionally substituted amino, and p represents an integer of 0 to 2;
r represents an integer of 0 to 2;
ring C represents an optionally substituted nitrogen-containing heterocyclic ring;
X represents a carbon atom or a nitrogen atom;
Y represents a bond or a lower alkylene group which may be substituted by an oxo;
Ar^1 and Ar^2 each represents an optionally substituted aromatic group; and

of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, (25) 5- to 10-membered aromatic heterocyclic group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, (26) acyloxy, (27) phthalimido which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon

and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, (24) C_{6-10} aryloxy which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, (25) 5- to 10-membered aromatic heterocyclic group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6}

selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino, (28) C_{1-6} alkoxy-C_{1-6} alkoxy, (29) mono-C_{7-16} aralkylamino and (30) di-C_{7-16} aralkylamino, and
(iv-2) a 5- to 10-membered heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated 3- to 6-membered cycloalkyl which may contain as ring-constituting atoms 1 or 2 hetero atoms selected from oxygen and sulfur atoms in addition to carbon atoms, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino or
(v) a 3- to 7-membered saturated cyclic amino.

10. A compound of Claim 8, wherein W is a divalent group of the formula: $-NR^6-CO-$ or $-CH_2-NR^6-CO-$ wherein R^6 is as defined in Claim 8.

11. A compound of Claim 8, wherein r is 0.

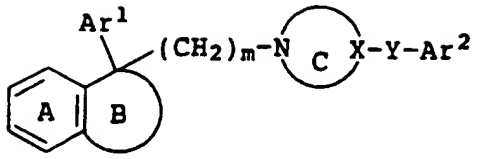
halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 7-membered saturated cyclic amino, formyl, acyl, acylamino, carboxy, carbamoyl, sulfo, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{6-10} aryl, C_{6-10} aryloxy, acyloxy, C_{1-6} alkoxy-C_{1-6} alkoxy, mono-C_{7-16} aralkylamino and di-C_{7-16} aralkylamino.

17. A compound of Claim 8, wherein m is 1 or 2.

18. A compound of Claim 8, wherein ring A is a benzene ring;
W is a divalent group of the formula: $-NR^6-CO-$ or $-CH_2-NR^6-CO-$,
wherein R^6 is a mono- or di-C_{1-6} alkylamino or a C_{1-6} alkyl which may be substituted by a 3- to 7-membered saturated cyclic amino,
r is 0,
ring C is a 6-membered nitrogen-containing heterocyclic ring containing 1 or 2 nitrogen atoms which may be oxidized, in addition to carbon atoms, which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl and carboxy,
Y is a bond,
Ar^1 is a phenyl or pyridyl which may be substituted by 1 to 3 halogen atoms,
Ar^2 is a phenyl or 5- or 6-membered aromatic heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl,

wherein $R^{5'}$ is a hydrogen atom, cyano, hydroxy or C_{1-6} alkyl-carbonyl, and t is 0 or 1,
Y is a bond,
Ar^1 is a phenyl,
Ar^2 is a phenyl or pyridyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, nitro, cyano, optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono- or di-C_{1-6} alkylamino, mono-C_{1-6} alkyl-carbonylamino, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, and
m is 2.

20. A compound of Claim 8, which is
1,3-dihydro-1-ethyl-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one,
1,3-dihydro-1-ethyl-3-(2-(4-hydroxy-4-phenylpiperidino)ethyl)-3-phenyl-2H-indol-2-one,
2-methyl-3-oxo-4-phenyl-4-(2-(4-phenylpiperidino)ethyl)-1,2,3,4-tetrahydroisoquinoline,
1-ethyl-1,3-dihydro-3-phenyl-3-(2-(4-(3-trifluoromethylphenyl)piperidino)ethyl)-2H-indol-2-one,
3-(2-(4-(3-chlorophenyl)piperazin-1-yl)ethyl)-1-ethyl-1,3-dihydro-3-phenyl-2H-indol-2-one,
3-(2-(4-cyano-4-phenylpiperidino)ethyl)-1-ethyl-1,3-dihydro-3-phenyl-2H-indol-2-one,
2-ethyl-4-(2-(4-(o-methoxyphenyl)piperazin-1-yl)ethyl)-3-oxo-4-phenyl-1,2,3,4-tetrahydroisoquinoline,
1,3-dihydro-1-(dimethylamino)-3-(2-(4-(o-methoxyphenyl)piperazin-1-yl)ethyl)-3-phenyl-2H-indol-2-one,
1,3-dihydro-1-(2-(morpholino)ethyl)-3-phenyl-3-(2-(4-phenylpiperidino)ethyl)-2H-indol-2-one,
1-ethyl-1,3-dihydro-3-phenyl-3-(2-(4-(3-trifluoromethylphenyl)piperazin-1-yl)ethyl)-2H-indol-2-one,
or a salt thereof.



wherein ring A represents an optionally substituted benzene ring;
ring B represents an optionally substituted 4- to 7-membered carbocyclic or heterocyclic ring;
ring C represents an optionally substituted nitrogen-containing heterocyclic ring;
X represents carbon atom or nitrogen atom;
Y represents a bond or a lower alkylene which may be substituted by an oxo;
Ar^1 and Ar^2 each represents an optionally substituted aromatic group; and
m represents an integer of 1 to 3, or a salt thereof for the manufacture of a pharmaceutical composition for controlling micturition.

INTERNATIONAL SEARCH REPORT

national application No.
PCT/JP 97/02447

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos..
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 28
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see annex

3. [ ] Claims Nos..
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees

Information on patent family members

International Application No
PCT/JP 97/02447

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 452809 A	23-10-91	AT 109003 T	15-08-94
		AU 641747 B	30-09-93
		AU 7506591 A	24-10-91
		CA 2040680 A	19-10-91
		DE 69103068 D	01-09-94
		DE 69103068 T	05-01-95
		JP 2500821 B	29-05-96
		JP 5009118 A	19-01-93
		US 5202331 A	13-04-93